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Article

Towards ^{99m}Tc - and Re-Based Multifunctional Silica Platforms for Theranostic Applications

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Abstract: Taking advantage of the radiation properties of ^{99m}Tc and $^{186/188}\text{Re}$ and the photophysical characteristics of the $\{\text{M}(\text{CO})_3\}^+$ moiety ($\text{M} = \text{Re}$), we developed a multifunctional silica platform with the theranostic pair $^{99m}\text{Tc}/\text{Re}$ with high potential for (nano)medical applications. Starting with a general screening to evaluate the most suitable mesoporous silica construct and the development of appropriate chelate systems, multifunctional mesoporous silica microparticles (SBA-15) were synthesized. These particles act as a model towards the synthesis of the corresponding nanoconstructs. The particles can be modified at the external surface with a targeting function and labeled with the $\{\text{M}(\text{CO})_3\}^+$ moiety ($\text{M} = ^{99m}\text{Tc}$, Re) at the pore surface. Thus, a silica platform is realized, whose bioprofile is not altered by the loaded modalities. The described synthetic procedures can be applied to establish a target-specific theranostic nanoplateform, which enables the combination of fluorescence and radio imaging, with the possibility of radio- and chemotherapy.

Keywords: technetium; rhenium; complexes; mesoporous silica; MCM-41; SBA-15; theranostic; multimodality; radioprobe

1. Introduction

For many decades, the nuclear isomer technetium-99m (^{99m}Tc , $t_{1/2} = 6\text{ h}$, $E_\gamma = 141\text{ keV}$) has been the most frequently used radio metal for applications in nuclear medical diagnostics [1–5]. In combination with isotopes 186 and 188 of its heavier homolog rhenium ($^{186/188}\text{Re}$), it represents one of the first “theranostic pairs” for nuclear medical diagnosis and therapy [6]. Recently, a conceptual extension of the “theranostic pair” Tc/Re was described by the combination of a ^{99m}Tc -based bio-mimetic with its organometallic but non-radioactive rhenium homologue [7]. The rhenium complex should be therapeutically active through its structure, while the ^{99m}Tc homologue allows for visualizing the pharmacology. Besides the use of Tc and Re as a “theranostic pair”, Stephenson et al. demonstrated that the two homologues allow the development of multimodal imaging probes [8]. A fluorescent Re -complex and the analogous ^{99m}Tc -complex provide the direct combination of optical imaging with high spatial resolution (in vitro) and radioimaging with sensitive detection of biological processes deep in the body (in vivo). By combining the multimodality of the $\{\text{M}(\text{CO})_3\}^+$ moiety ($\text{M} = ^{99m}\text{Tc}$, Re) with the theranostic properties of the $^{99m}\text{Tc}/^{186/188}\text{Re}$ pair, a multifunctional system is realized, which can be applied for diagnosis (radio and UV imaging) and (radio) therapy. This represents a new strategy for the application of Tc and Re in medicine and will enable new opportunities for these two elements. To apply multimodality probes in medicine, they have to be target-specific. To design a target-specific molecular

scaffold that combines all of the described Tc/Re-based modalities is challenging. Attractive alternatives are target-specific mesoporous nanoplateforms, which can incorporate the different modalities. An advantage of this approach is that the bioprofile of the target-specific mesoporous nanoplateform is not altered by the incorporated modality (Figure 1).

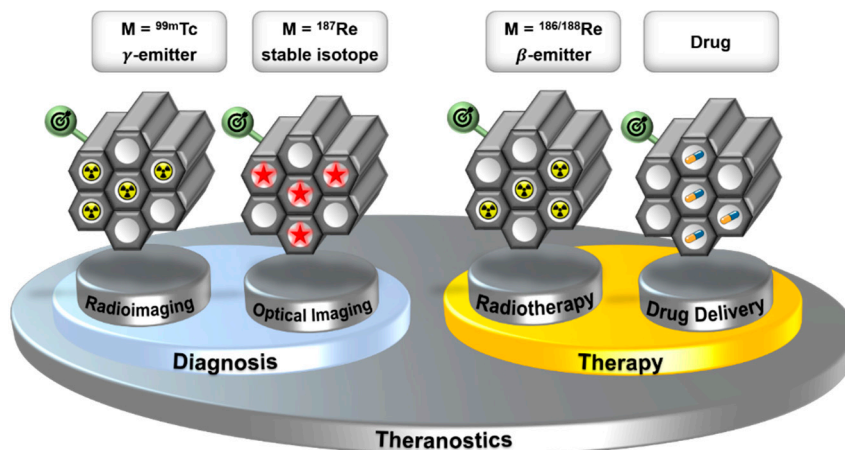


Figure 1. Target-specific mesoporous silica (nano)particles as a multifunctional platform, using the “theranostic pair” Tc/Re. The incorporated modalities can be changed without altering the bioprofile of the construct.

Currently, multifunctional nanoplateforms are a focus in nanomedicine [9]. Nanoparticles are ideal for combining different modalities and exhibit several advantages as compared to traditional diagnostic and therapeutic methods. They can easily integrate more than one kind of imaging or therapeutic agent. Large amounts of imaging agents or drugs can be introduced through chemical conjugation or simple loading due to the large surface area or interior cargo volume of the nanoparticles. Moreover, nanoparticles can target disease sites for drug delivery and imaging through physicochemical optimization of size and surface properties, and especially through the attachment of specific targeting moieties. Alteration of physicochemical properties can also be used to optimize the circulation time in the blood [10]. A further interesting feature of nanoparticles in radiopharmacy is the possibility to accumulate more than one radioactive moiety per target receptor. This leads to higher activity at the target site (amplification effect) as compared to directly labeled targeting molecules, which can only deliver one radioactive moiety per target receptor [11]. These beneficial properties of nanoparticles lead to a better contrast of the diagnostic image. The overall radioactivity can be reduced, leading to lower dose rates for the patients. In the past, different nanomaterials have been labeled with ^{99m}Tc in a nonspecific fashion, such as magnetic nanoparticles [12–15], organo-germanium compounds [16], carbon nanotubes [17], fullerene derivatives [18], polymers [19], pullulan acetates [20], chitosans [21,22], and tripalmitins [23]. In all these approaches, $[\text{}^{99m}\text{TcO}_4]^-$ activity has been reduced in the presence of the nanoparticles. This leads to a random distribution of ^{99m}Tc at the surface of the nanoparticles and an undefined binding mode at the particle surface. This unspecific labeling method is fast, but unambiguous characterization of the labeled nanoparticles is challenging. For the preparation of well-defined mesoporous nanoparticles, whose external and pore surface can be addressed independently at different stages of the synthesis, a specific and reproducible method to bind technetium and rhenium is required. Furthermore, developing a well-defined labeling procedure for nanoparticles with ^{99m}Tc can serve as a useful tool to investigate general aspects of nanoparticles, such as entry routes, pharmacokinetics, and the molecular mechanism of nanoparticle toxicity [24].

Mesoporous silica particles show highly interesting properties that make them promising candidates for target-specific, multifunctional nanoplateforms (Figure 1). Especially, selective functionalization of the external and the pore surface area as well as cargo loading are established features for this type of material [25–29]. Besides applications in catalysis [30–35] and sensing [36], MCM-41 (Mobil Composition

of Matter No. 41), a prominent representative of mesoporous silica particles, was first proposed as a drug delivery system in 2001 [37]. Since then, extensive research efforts have been dedicated to this subject, leading to sophisticated systems for drug delivery and controlled drug release [38–43]. Therefore, mesoporous silica particles enable the development of carrier systems, which combine targeting moieties, Tc- and Re-based imaging functions (radio- or UV-labels), and drug loading in a well-defined way. This creates multifunctional nanoplatforms, which are extremely suited for future applications in the evolving field of nanomedicine and personalized medicine [44].

Herein, we describe the development of a Tc and Re based multifunctional silica microplatform. This platform acts as a model towards the synthesis of the corresponding nanoconstructs. Starting with a general screening of different mesoporous silica microparticles to evaluate the most suitable construct and the development of appropriate chelate systems, multifunctional mesoporous silica particles, such as SBA-15 (Santa Barbara Amorphous type material No. 15) and spherical SBA-15 (sSBA-15), are synthesized. These particles can be labeled with the $\{M(\text{CO})_3\}^+$ moiety ($M = {}^{99\text{m}}\text{Tc}$, Re) at the pore surface.

2. Results and Discussion

2.1. Evaluation of Mesoporous Silica Particles

The term mesoporous silica represents a large family of compounds with a plethora of properties. To understand which type of mesoporous silica particle is suitable as a theranostic platform, in a first step a variety of different types of mesoporous silica microparticles, such as MCM-41 (Mobil Composition of Matter No. 41) [45], ASNCs (arrays of silica nanochannels) [46], and SBA-15 (Santa Barbara Amorphous type material No. 15) [47] were evaluated (for details see Supplementary Materials). All studied materials are established mesoporous silica microparticles. The screening was done by comparing the labeling performance of the functionalized silica microparticles, applying a new ${}^{99\text{m}}\text{Tc}$ labeling strategy [48,49]. The (3 + 2)-cycloaddition reaction of the $[{}^{99\text{m}}\text{TcO}_3(\text{tacn})]^+$ complex (tacn = 1,3,5-triazacacyclononane) with surface-grafted norbornene proceeds stereoselectively and with high reaction rates [50]. Therefore, it is an excellent method for fast and efficient screening of different materials. For this screening, 5-(bicycloheptenyl)triethoxysilane (NorboSi) was grafted to the surfaces of the silica particles under study in the first step. In the second step, $[{}^{99\text{m}}\text{TcO}_3(\text{tacn})]^+$ was reacted with these modified particles. Progress of labeling can be monitored by the decrease of the activity in the solution over time. Furthermore, the labeled particles were decomposed in 1M NaOH as control and the released activity was correlated to the observed decrease of activity in the solution by radio-HPLC. Figure 2 shows the labeling progress for two representative examples of the studied microparticles (MCM-41 and SBA-15).

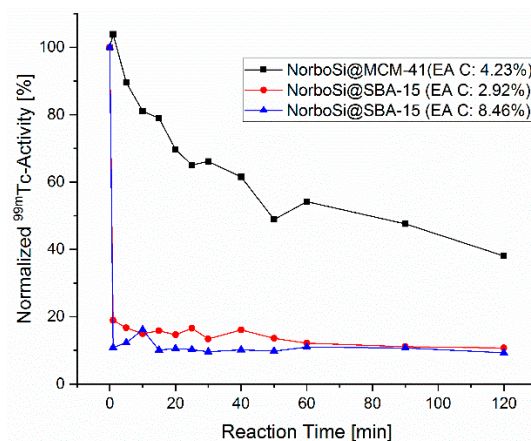


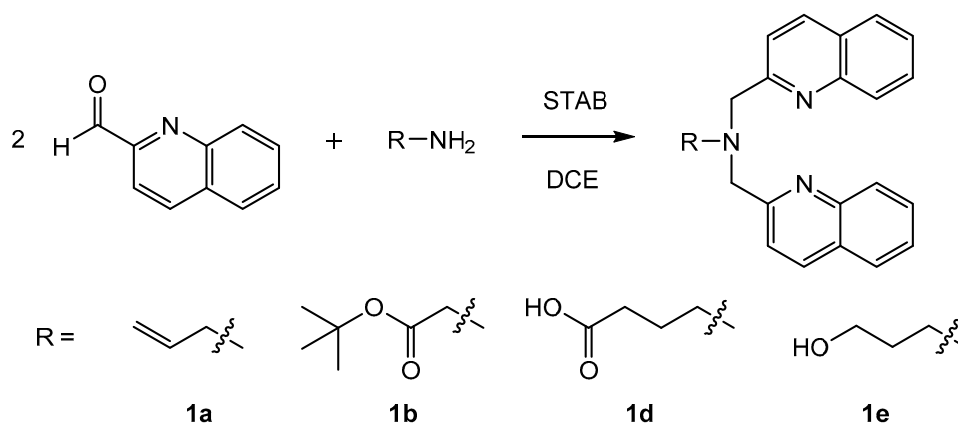
Figure 2. Labeling of NorboSi modified silica particles, NorboSi@MCM-41 (black), NorboSi@SBA-15 with low loading of functional groups (red), and NorboSi@SBA-15, with a high loading of functional

groups (blue). Percentages in brackets represent the carbon content of these particles, determined by elemental analysis (EA C). Conditions: 10 mg NorboSi modified silica particles suspended in 2 mL saline solution, addition of 2 mL $[^{99m}\text{TcO}_3(\text{tacn})]^+$ solution, sonication for 2 h, start temperature 25 °C (increased to 40 °C over the reaction time of 2 h).

The screening disclosed a remarkable difference in the labeling performance of the modified silica particles depending on the porosity. Whereas SBA-15 particles showed very fast and almost complete labeling (more than 90% labeling yield in less than 1 min reaction time), the MCM-41 particles had a much slower labeling rate. After 2 h reaction time, a labeling yield of only 60% was observed. Analysis of the gained data of all studied materials shows that silica particles with more accessible surface area lead to higher rates for the ^{99m}Tc -labeling. For mesoporous silica microparticles, most of the surface area (roughly 90%) is located in the pores. A larger pore diameter gives enhanced access for $[^{99m}\text{TcO}_3(\text{tacn})]^+$ to the norbornene decorated pores. As a consequence, particles with larger average pore size, such as SBA-15 (7–7.5 nm), show superior labeling performance as compared to particles with significantly smaller average pore size, such as MCM-41 (4 nm). The amount of grafted norbornenesilane (as determined by elemental analysis) has no significant influence as compared to the much more crucial pore size and accessible surface area. Due to the outstanding labeling performance of SBA-15 microparticles in contrast to all other tested silica particles, only this class of particles was considered for further investigation. In contrast to the synthetic procedure for SBA-15 microparticles, no synthetic procedures for well-defined SBA-15 nanoparticles are established. However, we expect that the herein reported procedures for the synthesis of bifunctionalized SBA-15 microparticles can be applied without further modifications for the synthesis of a SBA-15-based theranostic nanoplatform.

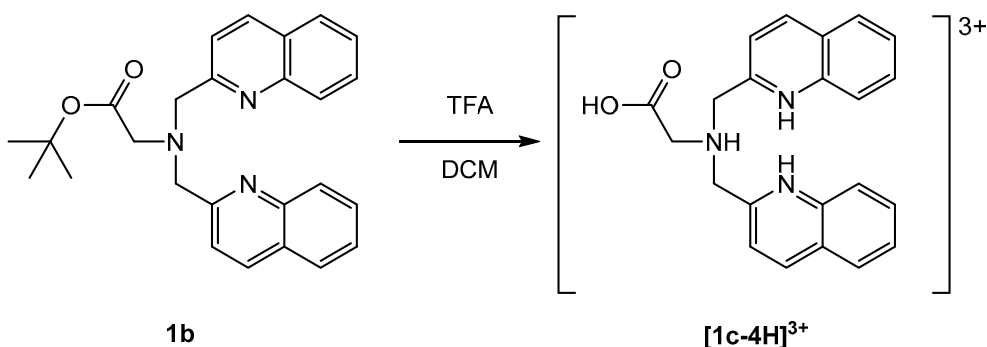
2.2. Synthesis of Chelators for Surface Modifications

By applying the (3 + 2)-cycloaddition $[^{99m}\text{TcO}_3(\text{tacn})]^+$ with alkenes, an efficient new method was established to study the accessibility of functional groups (NorboSi) at silica particle surfaces. However, the high-valent chemistry of the $\{^{99m}\text{TcO}_3\}^+$ was not established for theranostic applications due to the different redox potentials of the elements Tc and Re at their highest oxidation states [48]. This would limit a potential target-specific NorboSi@SBA-15 construct to radioimaging with ^{99m}Tc and conventional drug loading, disregarding the full potential of the theranostic pair $^{99m}\text{Tc}/\text{Re}$. Therefore, an alternative approach with the $\{\text{M}(\text{CO})_3\}^+$ core ($\text{M} = \text{Re}, ^{99m}\text{Tc}$) and SBA-15 particles was selected. For the development of theranostic nanoplatforms for (nuclear) medical applications, the bisquinoline/ $\{\text{M}(\text{CO})_3\}^+$ ($\text{M} = \text{Re}, ^{99m}\text{Tc}$) system is very well suited. The correlation of radioimaging and fluorescence studies with this system in single amino acid chelates was reported by Stephenson et al. [8]. SBA-15 particles carrying tridentate bisquinoline ligands enable the coordination of $\{^{99m}\text{Tc}(\text{CO})_3\}^+$ for radioimaging, $\{^{185/187}\text{Re}(\text{CO})_3\}^+$ for optical imaging, and $\{^{186/188}\text{Re}(\text{CO})_3\}^+$ for radiotherapy. Aiming at the synthesis of SBA-15 particles carrying bisquinoline chelates, a successive synthesis of the bisquinoline moiety (first by grafting of aminoalkyltriethoxysilane, followed by reductive amination with 2-quinolinecarboxaldehyde) at the SBA-15 surface is attractive. However, previous studies have shown that for this particular chelate, such a synthetic procedure does not lead to well-defined particles but generates a mixture of bi- and tridentate chelates at the silica surface [51]. Therefore, functionalization of SBA-15 by grafting of bisquinoline trialkoxysilanes is preferred. Different bisquinoline moieties with appropriate terminal substituents for the attachment of trialkoxysilanes have been synthesized (Scheme 1) in direct reductive amination.



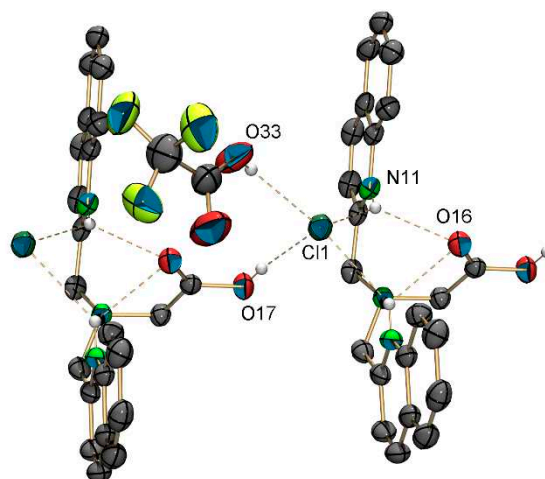
Scheme 1. Synthesis of different bisquinoline moieties with appropriate terminal substituents for the attachment of trialkoxysilanes. Reaction time was 2–25 h at room temperature. Note: STAB = sodium triacetoxymethylborohydride; DCE = 1,2-dichloroethane.

All compounds were isolated and characterized (see Supplementary Materials). The carboxyl group was introduced into the bisquinoline moiety by a one-step reaction with 4-aminobutyric acid (**1d**) or in a two-step procedure via deprotection of **1b** (Scheme 2).



Scheme 2. Deprotection of **1b** with TFA via microwave reaction for 20 min at 90 °C. Note: TFA = trifluoroacetic acid; DCM = dichloromethane.

The elemental composition of $[\text{1c-4H}](\text{TFA})_3$ suggested the formation of a three-fold positively charged cation ($[\text{1c-4H}]^{3+}$). Single crystals of $[\text{1c-3H}]\text{Cl}(\text{TFA})\cdot(\text{HTFA})$ were obtained by slow evaporation of a CDCl_3 solution of $[\text{1c-4H}](\text{TFA})_3$ (Figure 3). The chloride anion obviously originated from the solvent. In the structure of $[\text{1c-3H}]\text{Cl}(\text{TFA})\cdot(\text{HTFA})$, two trifluoroacetic acid (TFA) anions share one proton. The two quinoline nitrogen atoms are protonated and both form hydrogen bonds with a common chloride anion (3.2019 (14) Å). In this structure, a TFA molecule is protonated, while the aliphatic tertiary amine is not (for crystallographic details see Supplementary Materials). This finding is in contrast with the expected pK_a values of TFA and amines in solution. This rare structural motif of doubly-protonated pyridine rings pointing to a common hydrogen acceptor despite the presence of the more basic aliphatic nitrogen of the bispicolylamine has been described before [52,53].

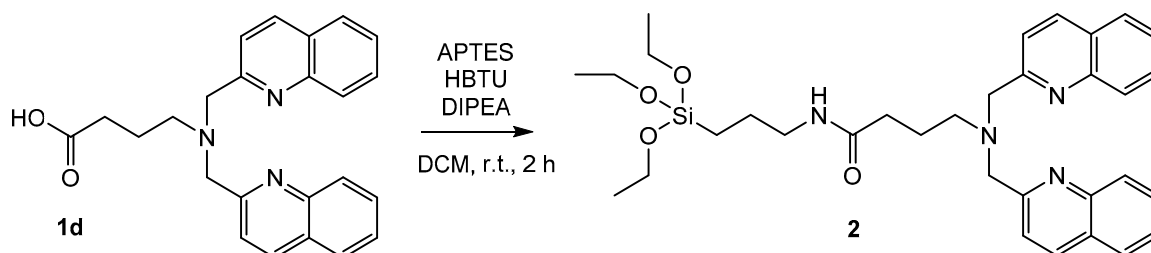


Symmetry operation: $x + 1, y, z$.

Figure 3. ORTEP representation [54] of the crystal packing of $[1c-3H]Cl(TFA) \cdot (HTFA)$, showing the important hydrogen bonds. Thermal ellipsoids represent 50% probability. One TFA anion and hydrogen atoms that are not involved in hydrogen bonds are omitted for clarity. Selected hydrogen bonds (D...A) [Å]: O17–Cl1 2.9763 (19), O33–Cl1 2.993 (4), N11–Cl1* 3.2019(14), N11–O16 3.0084 (17).

Positive electron density between the trifluoroacetate molecule and the chloride anion indicates that the TFA is protonated and forms a hydrogen bond with the chloride anion (O33–Cl1: 2.993 (4) Å). The distance of this hydrogen bond is typical for such carboxylic acid–chloride interactions [55]. The overall crystal packing and the local environment of two pyridinium units next to the amine and one chloride ion next to the TFA are all responsible for this rare structural feature.

The synthesized chelates can be coupled to trialkoxysilanes via hydrosilylation and cross-metathesis (**1a**), amide bond formation (**1c**, **1d**), or substitution reactions (**1e**). The amide bond formation of 3-aminopropyltriethoxysilane (APTES) with the acid bisquinoline moiety **1d** is the most efficient synthetic approach (Scheme 3).

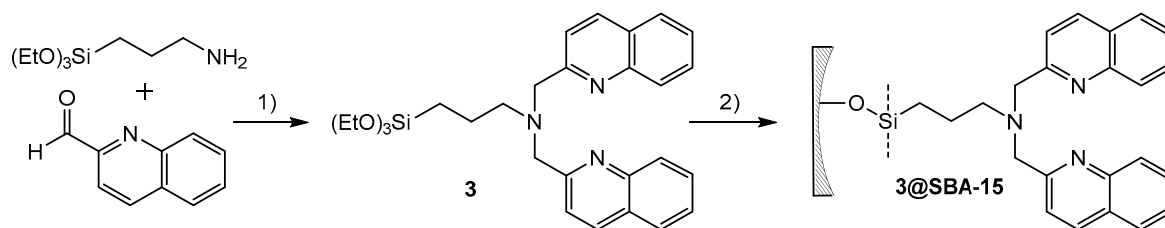


Scheme 3. Synthesis of **2** by amide bond formation of **1d** with 3-aminopropyltriethoxysilane (APTES) for 2 h at room temperature. Note: HBTU = 2-(1H-Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-hexafluorophosphate; DIPEA = *N,N*-Diisopropylethylamine.

The amide bond formation of APTES with a carboxylic acid represents a general strategy for the synthesis of functionalized trialkoxysilanes. It is fast and work up procedures are efficient. Extraction with dichloromethane (DCM) is sufficient to obtain the product in high purity. Tetramethylurea, the only side product, does not interfere with the subsequent grafting onto silica particles. As an alternative, the direct reductive amination of 2-quinolinecarboxaldehyde with APTES is a direct and efficient synthetic pathway (Scheme 4).

The ethoxysilane groups tend to hydrolyze and subsequently cross-link. This undesired side reaction has been addressed with EtOH for quenching of the residual reducing agent and C-18 flash chromatography purification. The isolated bisquinolinepropyltriethoxysilane (**3**) is stable as a solid

under ambient conditions over a period of several months. To evaluate the optimal reaction condition for the bifunctionalization of SBA-15 particles, compound **3** was grafted in high (160 M) and low (4 M) concentrations onto SBA-15 particles in dry toluene (Scheme 4).



Scheme 4. Synthesis of **3** by reductive amination of 2-quinolinecarboxaldehyde with 3-aminopropyltriethoxysilane in the presence of sodium triacetoxyborohydride (3.5 h, room temperature). Subsequent grafting of **3** to SBA-15 particles (2 h sonication, 60 °C).

The intact porous network of the modified SBA-15 particles (**3@SBA-15**) and successful grafting to the external surface as well as to the pore surface was confirmed by determining the decrease of the pore volume, the average pore diameter, and the total specific surface area (Table 1).

Table 1. N₂-sorption values for SBA-15 and **3@SBA-15** particles, which contain 0.37 mmol **3**/g particles (determined by elemental analysis).

Particles	Average Pore Size [nm]	Total Pore Volume [cm ³ /g]	BET Surface Area [m ² /g]
SBA-15	7.0	0.75	570
3@SBA-15	6.8	0.64	441

The integrity of the grafted **3** was shown by decomposing the particles in 1M NaOD in D₂O and subsequent analysis of the solution by ¹H-NMR and HR-ESI MS (high resolution-electrospray ionization mass spectrometry); an analytical strategy that was recently developed by Farinha and coworkers [56]. HR-ESI and ¹H-NMR allowed for unambiguous characterization of the hydrolyzed form of **3** and showed the release of EtOD due to the hydrolysis of Si–OEt groups not involved in the binding to SBA-15. Quantification of the **3@SBA-15** particles with high **3** content by elemental analysis showed 0.37 mmol of **3** per g of SBA-15, which correlates to 0.33 molecules of **3** per nm² surface of SBA-15. For comparison, applying **3** in lower concentrations for the synthesis led to **3@SBA-15** particles containing 0.08 mmol **3** per g particles.

Since **3** is highly stable, an alternative method for the synthesis of **3@SBA-15** is the co-condensation approach. This led to microparticles showing high loading and homogeneous distribution of the functionality over the complete porous network. Detailed synthetic procedures for all syntheses are described in the supplementary.

2.3. Reactions of Bisquinoline Molecules with the {M(CO)₃}⁺ Moiety (M = Re, ^{99m}Tc)

The chelates **1a**, **1b**, **1e**, and **3** were reacted with (NEt₄)₂[ReBr₃(CO)₃] and the products [(**1a**)Re(CO)₃]⁺, [(**1b**)Re(CO)₃]⁺, [(**1e**)Re(CO)₃]⁺, and [(**3**)Re(CO)₃]⁺ (**3-Re**) were isolated and fully characterized. Single crystals, suitable for X-ray diffraction analysis, were obtained for [(**1a**)Re(CO)₃](PF₆), [(**1b**)Re(CO)₃](PF₆) and [(**1e**)Re(CO)₃](PF₆) by vapor diffusion (Figure 4).

Furthermore, the photophysical properties of **3-Re** were studied. The UV–Vis spectrum of **3-Re** shows a maximum absorbance at 323 nm with an extinction coefficient of 13696 M^{−1}·cm^{−1} in CHCl₃ under ambient conditions. The emission spectrum shows two distinct emissions at 426 and 546 nm. These data are in good agreement with Stephenson et al [8]. Under an inert gas atmosphere (N₂), two emission maxima at 383 and 566 nm can be observed. The lifetime of the excited state determined in

CHCl_3/N_2 is 12.5 μs . This is long enough to enable time-gating techniques, which are necessary to overcome interferences from endogenous fluorescence during in vitro imaging studies [8].

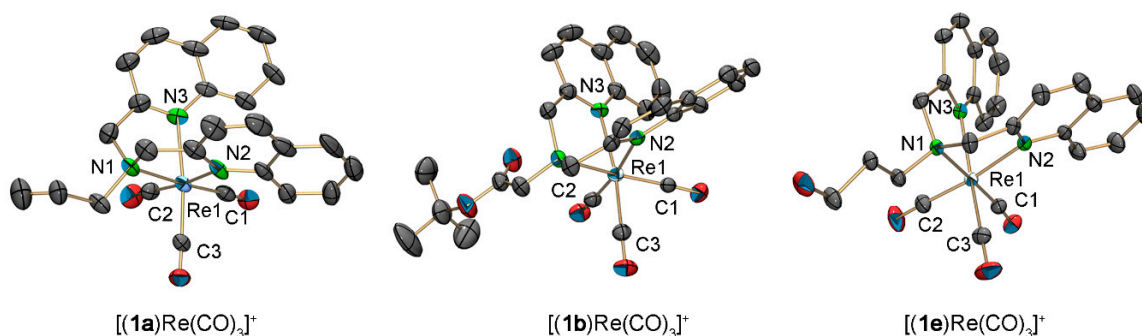
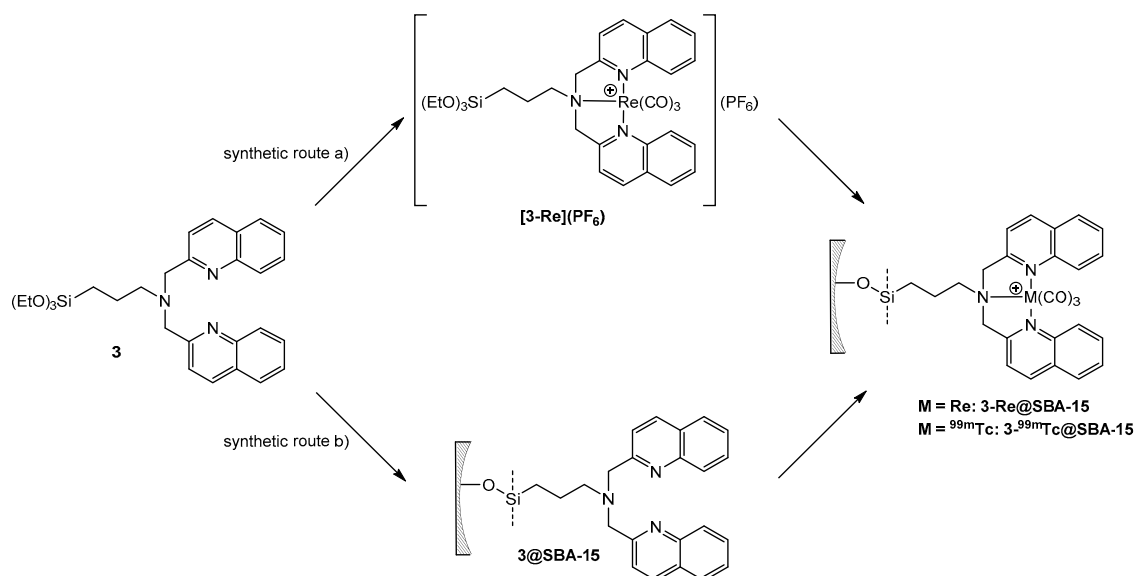


Figure 4. ORTEP representation [54] of the $[(1\mathbf{a})\text{Re}(\text{CO})_3]^+$, $[(1\mathbf{b})\text{Re}(\text{CO})_3]^+$, and $[(1\mathbf{e})\text{Re}(\text{CO})_3]^+$ cations of the crystal structure of $[(1\mathbf{a})\text{Re}(\text{CO})_3](\text{PF}_6)$, $[(1\mathbf{b})\text{Re}(\text{CO})_3](\text{PF}_6)$, and $[(1\mathbf{e})\text{Re}(\text{CO})_3](\text{PF}_6)$. Thermal ellipsoids represent 50% probability. Hydrogen atoms are omitted for clarity. Selected bond lengths [\AA] and angles [$^\circ$]: $[(1\mathbf{a})\text{Re}(\text{CO})_3](\text{PF}_6)$, Re1–C1 1.899 (5), Re1–C2 1.925 (5), Re1–C3 1.909 (5), Re1–N1 2.199 (5), Re1–N2 2.218 (4), Re1–N3 2.207 (4), C1–Re1–C2 86.7 (2), C1–Re1–C3 83.1 (2), N1–Re1–N2 75.70 (16), N1–Re1–N3 79.49 (19); $[(1\mathbf{b})\text{Re}(\text{CO})_3](\text{PF}_6)$, Re1–C1 1.915 (4), Re1–C2 1.918 (4), Re1–C3 1.927 (4), Re1–N1 2.230 (3), Re1–N2 2.224 (3), Re1–N3 2.216 (3), C1–Re1–C2 88.94 (16), C1–Re1–C3 84.06 (15), N1–Re1–N2 73.64 (11), N1–Re1–N3 78.71 (11); $[(1\mathbf{e})\text{Re}(\text{CO})_3](\text{PF}_6)$, Re1–C1 1.909 (2), Re1–C2 1.920 (3), Re1–C3 1.914 (3), Re1–N1 2.2282 (17), Re1–N2 2.2391 (18), Re1–N3 2.2164 (18), C1–Re1–C2 83.09 (10), C1–Re1–C3 84.93 (10), N1–Re1–N2 77.14 (7), N1–Re1–N3 78.61 (7).

Grafting of **3-Re** onto SBA-15 particles or solid phase supported reaction of **3@SBA-15** with $[\text{Re}(\text{H}_2\text{O})_3(\text{CO})_3]^+$ results in **3-Re@SBA-15** particles (Scheme 5). HPLC of the reaction solution of the reaction of **3-Re** with SBA-15 particles (route a)) did not show any release of $[\text{Re}(\text{H}_2\text{O})_3(\text{CO})_3]^+$. Therefore, it can be assumed that this reaction yields **3-Re@SBA-15** particles, which do not contain uncoordinated **3**. This was confirmed by the addition of $[\text{Re}(\text{H}_2\text{O})_3(\text{CO})_3]^+$ to these particles, which did not lead to a labeling of the particles. However, in the context of potential nuclearmedical applications, synthetic route a) would require a two-step procedure, starting with the synthesis of **3- $^{186/188}\text{Re}$** , followed by the grafting process. The increased complexity of this synthetic procedure reduces its potential for clinic applications. From a theranostic point of view, the second approach (synthetic route b)) has higher relevance due to a one-step labeling procedure. Aiming to establish a feasible labeling for medical applications with the radio isotopes $^{186/188}\text{Re}$ and $^{99\text{m}}\text{Tc}$, $[\text{Re}(\text{H}_2\text{O})_3(\text{CO})_3]^+$ was chosen as a precursor for these reactions. In contrast to $[\text{Re}(\text{Br})_3(\text{CO})_3]^+$, this precursor allows for a direct translation of the model reaction with $[\text{Re}(\text{H}_2\text{O})_3(\text{CO})_3]^+$ into a labeling procedure with $[\text{Re}(\text{H}_2\text{O})_3(\text{CO})_3]^+$ and $[\text{Re}(\text{H}_2\text{O})_3(\text{CO})_3]^+$. Labeling of **3@SBA-15** particles, which contained 0.08 mmol **3/g** particles (determined by EA) with an excess of $[\text{Re}(\text{H}_2\text{O})_3(\text{CO})_3]^+$, yielded **3-Re@SBA-15** particles with an Re loading of 0.077 mmol/g particles (determined by ICP-MS). The incomplete occupation of the bisquinoline ligands at the surface of these fluorescent **3-Re@SBA-15** particles allows for subsequent labeling with $[\text{Re}(\text{H}_2\text{O})_3(\text{CO})_3]^+$ in a second step (detail see Supplementary Figure S4.4.3). For both synthetic routes, the CO bands in the IR spectrum clearly indicate successful coordination of the $[\text{Re}(\text{CO})_3]^+$ core (Figure 5). The CO vibrations of **3-Re@SBA-15** (2026, 1901, and 1981 cm^{-1}) are in good agreement with the vibrations found for the **3-Re** (2025 and 1901 cm^{-1} , Supplementary Figure S4.2.4.1). For comparison, the CO vibrations of the precursor complexes $[\text{ReBr}_3(\text{CO})_3]^{2-}$ and $[\text{Re}(\text{H}_2\text{O})_3(\text{CO})_3]^+$ can be observed at 1997 and 1844, and 2037 and 1916 cm^{-1} , respectively [57]. The intensive bands at 1043 cm^{-1} can be assigned to Si–O vibrations of the bulk material.

The labeling of **3@SBA-15** with $[\text{Re}(\text{H}_2\text{O})_3(\text{CO})_3]^+$ (Scheme 5, synthetic route b)) to yield **3- $^{99\text{m}}\text{Tc}$ @SBA-15** was fast, with a labeling yield > 99%. Detailed information for this labeling procedure can be found in the Supplementary Materials (Supplementary Figure S4.3.4). As for the screening of different silica materials, the labeling progress was indirectly analyzed by determining the decrease

of activity in the solution. Prior to the reaction, radio-HPLC of the solution shows a clear signal for the $[^{99m}\text{Tc}(\text{H}_2\text{O})_3(\text{CO})_3]^+$ complex at 5.5 min (Figure 6). After 15 min at 100 °C (microwave), coordination of the $\{^{99m}\text{Tc}(\text{CO})_3\}^+$ onto the silica particles was confirmed by radio-HPLC. In addition, gamma counting of the filtered reaction solution showed a decrease of activity in the solution to almost background level. Since **3** is randomly distributed over the surface of these model particles, the labeling with ^{99m}Tc is not preferential in the pores.



Scheme 5. Synthesis of silica particles “loaded” with Re via (a) grafting of **3-Re** or (b) solid phase supported synthesis. Synthetic route (b) corresponds to the labeling of the silica particles with ^{99m}Tc .

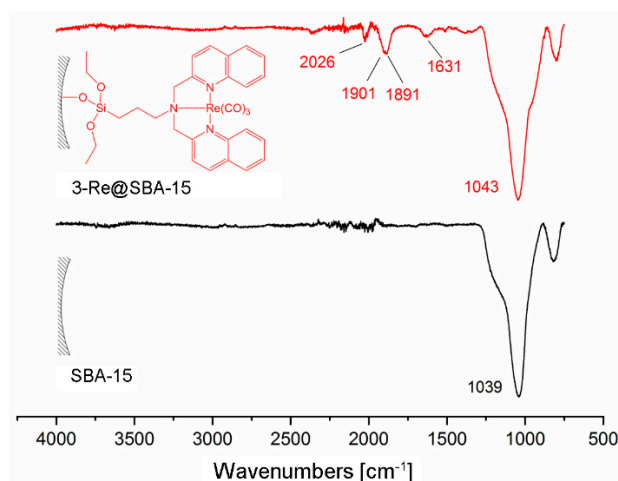


Figure 5. Comparison of the IR spectra of SBA-15 particles (black) and **3-Re@SBA-15** particles (red), synthesized by the reaction of $[\text{Re}(\text{H}_2\text{O})_3(\text{CO})_3]^+$ with **3@SBA-15** (synthetic route b in Scheme 5). The CO vibrations at 2026, 1901, and 1891 cm^{-1} show the coordination of the $[\text{Re}(\text{CO})_3]^+$ moiety to **3**.

2.4. Synthesis and Labeling of a Bifunctional SBA-15 Construct with Re and ^{99m}Tc

For the synthesis of a novel (nano)platform for theranostic applications, a bifunctionalized SBA-15 microparticle model construct was realized. In the synthesized model, a fluorescent dye, grafted preferentially to the external surface of the SBA-15 particles, mimics the targeting function. This was achieved with short reaction time, an apolar solvent (hexane), and a directing silane, such as 3-aminopropyltrimethoxyethoxyethoxysilane (APTMEES) [26]. Accordingly, the average pore size of the SBA-15 particles remained invariant upon the grafting of APTMEES (see Supplementary Materials)

in contrast to the grafting of **3** to unmodified SBA-15 particles. Subsequently, the grafted amino groups of APTMEES were reacted with the red emitting dye eosin isothiocyanate (EOITC). In the third step, **3** was grafted to the SBA-15 particles at the still accessible surface. Finally, the bifunctionalized EOITC/**3**@SBA-15 particles were labeled with the $\{M(CO)_3\}^+$ ($M = Re, {}^{99m}Tc$) precursors (Scheme 6).

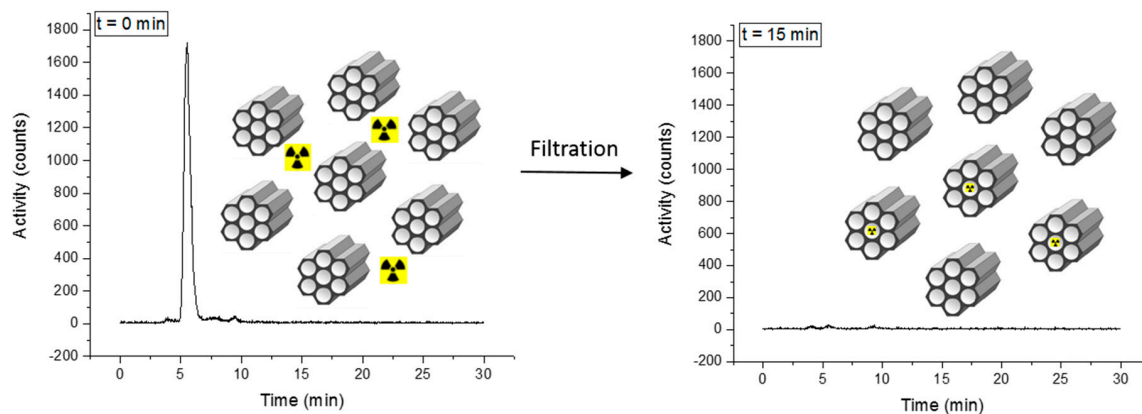
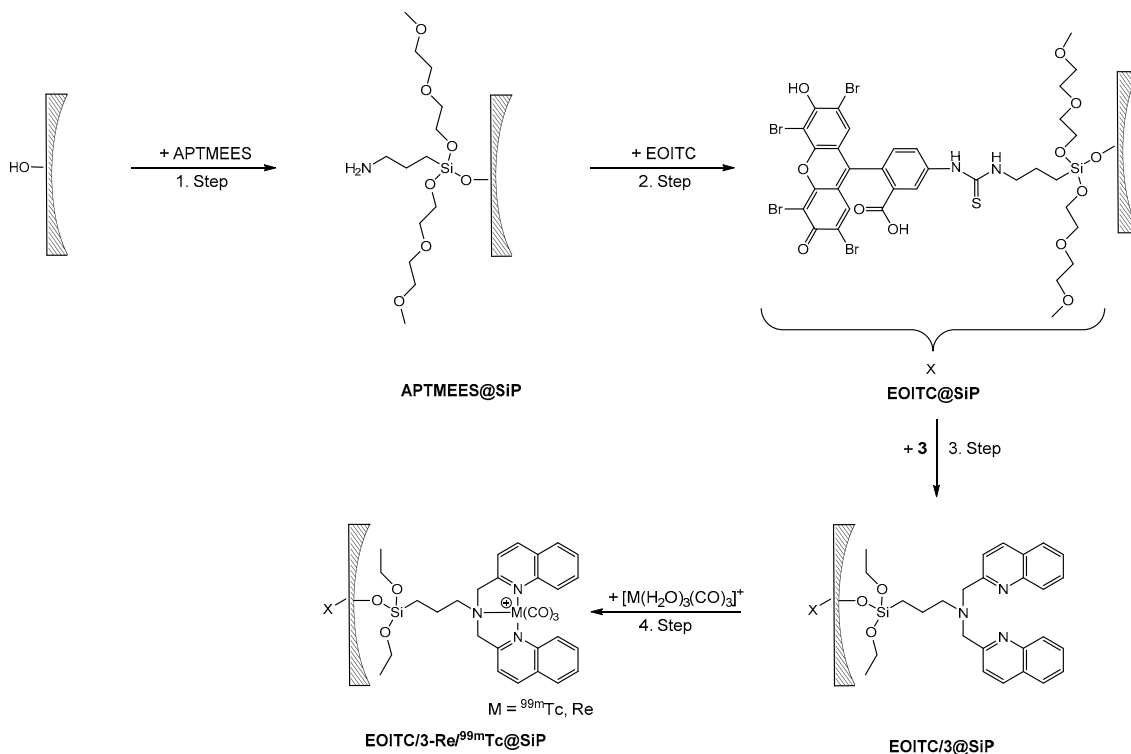


Figure 6. Idealized picture of the labeling of **3**@SBA-15 with $[{}^{99m}Tc(H_2O)_3(CO)_3]^+$. Since **3** is randomly distributed over the surface of these model particles, the labeling with ${}^{99m}Tc$ is not preferential in the pores. The radio-HPLC traces show the activity in the reaction solution. Left: The γ -signal of $[{}^{99m}Tc(H_2O)_3(CO)_3]^+$ is observed at 5.5 min (reaction time = 0). Right: almost quantitative coordination of $[{}^{99m}Tc(H_2O)_3(CO)_3]^+$ at the **3**@SBA-15 particles (reaction time = 15 min) evidenced by disappearance of the 5.5 min peak.



Scheme 6. Synthesis of bifunctionalized SBA-15 particles (SiP = SBA-15, spherical SBA-15 (sSBA-15)). Step 1: Grafting of APTMEES (10 min, room temperature). Step 2: Coupling of the fluorescent dye eosin isothiocyanate (EOITC) to the surface-grafted amino groups (16 h, room temperature). Step 3: Grafting of **3** (2 h, 40 °C). Step 4: Labeling of the **EOITC/3**@SBA-15 particles with $\{M(CO)_3\}^+$ ($M = Re, {}^{99m}Tc$) precursors (pH 7; Re: 45 min, 100 °C; ${}^{99m}Tc$: 15 min, 100 °C).

Confocal laser scanning microscopy (CLSM) images of spherical SBA-15 (sSBA-15) prepared according to Scheme 6 show the location of the fluorescent moiety within the particles (Figure 7).

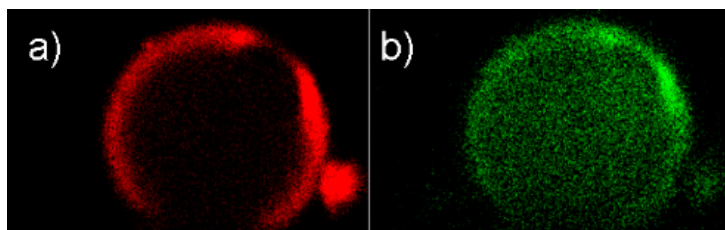


Figure 7. Selective bifunctionalization of sSBA-15 particles visualized by confocal laser scanning microscopy (CLSM): (a) red emission of the EOITC dye; (b) green emission of the **3-Re** complex.

By choosing different excitation wavelengths, the two moieties EOITC and **3-Re** can be excited separately in the same particle. Optical slices in the center of the particles were selected and representative images are shown in Figure 7. The red emission assessed the preferential attachment of EOITC on the external surface. The “loading” of the $\{\text{Re}(\text{CO})_3\}^+$ complex to the pore surface is depicted by the green emission of the **3-Re** complex. Finally, the bifunctional **EOITC/3@sSBA-15** particles were labeled with $[\text{}^{99\text{m}}\text{Tc}(\text{H}_2\text{O})_3(\text{CO})_3]^+$ (Scheme 6, step 4). The reaction of $[\text{}^{99\text{m}}\text{Tc}(\text{H}_2\text{O})_3(\text{CO})_3]^+$ with **EOITC/3@sSBA-15** (5–15 MBq, pH 7, 15 min, 100 °C, microwave) led to labeling yields of 79%. Benchmarking this result, monofunctionalized particles that contained only **3** (**3@sSBA-15**) were reacted with $[\text{}^{99\text{m}}\text{Tc}(\text{H}_2\text{O})_3(\text{CO})_3]^+$ under the same labeling conditions, with a yield of 80%. The lower labeling yield of the **3@sSBA-15** particles (80%) vs. the **3@SBA-15** particles (>99%) described earlier in this report can be rationalized by the broader pore size distribution of the sSBA-15 particles. However, sSBA-15 particles had to be utilized to visualize the selective functionalization of the silica particles by CLSM. Further labeling studies of $[\text{}^{99\text{m}}\text{Tc}(\text{H}_2\text{O})_3(\text{CO})_3]^+$ with the precursor particles **APTMEES/3@sSBA** (Scheme 6, step 1), showed a labeling yield of only 68%. The decrease of 11% labeling yield (**APTMEES/3@sSBA** vs. **EOITC/3@sSBA-15**) has to be ascribed to electrostatic repulsion of the positively charged $[\text{}^{99\text{m}}\text{Tc}(\text{H}_2\text{O})_3(\text{CO})_3]^+$ molecules and the protonated amines of the APTMEES (saline solution, pH 7).

We show in this feasibility study synthetic pathways and procedures towards a SBA-15-based target-specific theranostic nanoplatform, utilizing the theranostic pair $^{99\text{m}}\text{Tc}/\text{Re}$. This platform enables the combination of optical (fluorescence) and radio imaging with radio- and chemotherapy. The translation into a theranostic nanoplatform can be realized as soon as procedures for the synthesis of well-defined, non-agglomerated SBA-15 nanoparticles have been established.

3. Materials and Methods

Caution: $^{99\text{m}}\text{Tc}$ is a γ -emitter. All experiments have to be performed in laboratories approved for working with low-level radioactive materials.

All chemicals were of reagent-grade quality or higher and were obtained from commercial suppliers. Solvents were used as received or dried over molecular sieves. $\text{Na}[\text{}^{99\text{m}}\text{TcO}_4]$ in 0.9% saline was eluted from a $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ Ultra-Technekow FM generator purchased from Mallinckrodt Medical B.V. (Petten, The Netherlands). $[\text{}^{99\text{m}}\text{Tc}(\text{H}_2\text{O})_3(\text{CO})_3]^+$ was synthesized according to an adapted version of a published procedure [58]. The $[\text{}^{99\text{m}}\text{TcO}_4]^-$ eluate (1–2 mL, obtained from the $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ generator) was added to a N_2 -flushed microwave vial containing $\text{Na}_2(\text{BH}_3\text{CO}_2)$ (4 mg, 0.040 mmol), disodium tartrate dihydrate (7.0 mg, 0.030 mmol), and disodium tetraborate pentahydrate (7 mg, 0.024 mmol), and heated in a microwave reactor for 10 min at 110 °C. Finally, the pH of the solution was adjusted to pH 7 by the addition of 80–100 μL 1 M HCl. The $[\text{}^{99\text{m}}\text{TcO}_3(\text{tacn})]^+$ was synthesized according a literature procedure [59].

Silica particles used in this study were of the MCM-41 and SBA-15 types. Due to their irregular morphological properties, such as size and shape, they are not suited for optical analysis by CLSM.

For that purpose, large spherical particles of the SBA-15 type (sSBA-15) were chosen. Besides these well-known microparticles of MCM-41 and SBA-15, hexagonal arrays of silica nanochannels (ASNCs), MCM-41-nanoparticles, and MCM-41 particles with various pore sizes were used in the initial screening. The particles were synthesized following literature procedures (sSBA-15 [26], ASNCs [60], all others [61]). Characteristics of the applied silica particles are summarized in table S1 in the supplementary information.

High-resolution mass spectrometry (HR-ESI-MS) was performed on a Bruker maXis QToF high-resolution mass spectrometer (Bruker GmbH, Bremen, Germany).

^1H and ^{13}C -NMR spectra were recorded in deuterated solvents on a Bruker AV-400 or Bruker AV-500 MHz spectrometer at 300 K. ^{13}C -NMR spectra were proton decoupled. The chemical shifts (δ) are reported in ppm relative to residual solvent peaks (dmf- d_7 : ^1H : 8.03 ppm, ^{13}C : 163.15 ppm; CDCl_3 : ^1H : 7.26 ppm, ^{13}C : 77.16 ppm; MeOD: ^1H : 3.31 ppm, ^{13}C : 49.00 ppm; Acetone- d_6 : ^1H : 2.05 ppm, ^{13}C : 29.84 ppm). The abbreviations for the peak multiplicities are as follows: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet), br (broad). ^{29}Si -NMR spectra were recorded on a Bruker AV-500 MHz.

Gamma-counting of the $^{99\text{m}}\text{Tc}$ solutions was performed on a COBRA 5002 (Packard Instrument, Meriden, USA). Half-life time corrections for the labeling of silica particles were neglected due to the sequential measurement of the samples, with less than 5 min between two samples. Labeling of silica particles: The initial activity of the $^{99\text{m}}\text{Tc}$ -solutions was determined prior to the addition of the particle suspension. According to the dilution (factor 2), the activity for $t = 0$ min was calculated.

HPLC analyses were performed on a Merck Hitachi LaChrom L 7100 pump coupled to a Merck Hitachi LaChrom L7200 tunable UV detector (Hitachi, Tokyo, Japan) and a radiodetector. UV-Vis detection was performed at 250 nm. The detection of radioactive $^{99\text{m}}\text{Tc}$ complexes was performed with a Berthold LB508 (Berthold Technologies, Bad Wildbad, Germany) radiodetector equipped with a bismuth germanium oxid (BGO) cell. Separations were achieved on a Macherey–Nagel C18 reversed-phase column (nucleosil 10 ml, 250/3 mm) using a gradient methanol (solvent A) and 0.1% trifluoroacetic acid (solvent B). Applied HPLC gradient: 0–3 min: 0% A, 100% B; 3–3.1 min: 0–25% A, 100–75% B; 3.1–9 min: 25% A, 75% B; 9–9.1 min: 25–34% A, 75–66% B; 9.1–18 min: 34–100% A, 66–0% B; 18–25 min: 100% A, 0% B; 25–25.1 min: 100–0% A, 0–100% B; 25.1–30 min: 0% A, 100% B. The flow rate was $0.5\text{ mL}\cdot\text{min}^{-1}$. Ultra performance liquid chromatography-electrospray ionization-mass spectrometry (UPLC-ESI-MS) was performed on a Waters Acquity UPLC System coupled to a Bruker high capacity ion trap mass spectrometer (HCTM), using an Acquity UPLC ethylene bridge hybrid (BEH) C18 $1.7\text{ }\mu\text{m}$ ($2.1 \times 50\text{ mm}$) column. UPLC solvents were formic acid (0.1% in millipore water) (solvent A) and acetonitrile HPLC grade (solvent B). Applied UPLC gradient: 0–0.5 min: 95% A, 5% B; 0.51–4.0 min: linear gradient from 95% A (5% B) to 0% A (100% B); 4–5 min: 100% B. The flow rate was $0.6\text{ mL}/\text{min}$. Detection was performed at 250 nm and 480 nm (diode-array detector). For preparative HPLC, a Varian ProStar 320 system (Varian Inc, Palo Alto, USA) was used with a Dr. Maisch Reprosil C18 100-7 ($40 \times 250\text{ mm}$) column. The solvents (HPLC grade) were 0.1% trifluoroacetic acid (solvent A) and acetonitrile (solvent B). Applied HPLC gradient: 0–2 min: 66% A (34% B); 2–45 min: linear gradient from 66% A (34% B) to 0% A (100% B); 45–51 min: 100% B. The flow rate was $40\text{ mL}/\text{min}$. Detection was performed at 235 nm.

IR spectra were recorded on a Perkin-Elmer FT-IR Spectrum Two spectrometer (Perkin-Elmer Inc., Waltham, USA), using ATR technique and applied as neat samples.

Nitrogen sorption isotherms were collected at 77 K using a Quantachrome NOVA 3000 (Quantachrome Instruments, Boynton Beach, USA). Samples were vacuum-degassed at $80\text{ }^\circ\text{C}$ for 3 h. The total specific surface area was calculated by the Brunauer-Emmett-Teller (BET) method [62]. Mesopore size distributions were evaluated by the nonlocal density functional theory (NLDT) method [63] developed for silica exhibiting cylindrical pore geometry (NOVAWin software, Version 11.0, Quantachrome Instruments, Boynton Beach, USA). The adsorption branch of the respective isotherm was used for the calculations.

The fluorescence and CLSM setup consisted of an Olympus BX60 microscope equipped with a FluoView FV300 confocal unit and lasers operating at 488 and 543.5 nm.

UV-Vis spectra were measured on a Cary 50 UV-Vis spectrometer or a SPECORD® 250 PLUS spectrometer (Analytik Jena, Jena, Germany) with solution samples in 1 cm quartz cells.; λ_{\max} (ϵ) in nm; ϵ in $\text{M}^{-1}\cdot\text{cm}^{-1}$. Fluorescence spectra were recorded with a LS 50 B Luminescence spectrometer (Perkin-Elmer Inc., Waltham, USA); λ_{em} (λ_{ex}) in nm. Lifetime and transient absorption measurements were recorded on a LP920-K laser flash photolysis transient absorption spectrometer using a flash-lamp-pumped, Q-switched Nd:YAG laser (355 nm) as the excitation source. Probing of the sample was conducted by a Xe920 probe lamp (450 W) and an xP920 pulsing unit module. Argon-purged solution samples in 1 cm quartz cells were used.

Microwave reactions were performed with a Biotage Initiator+ Robot Eight (Biotage, Uppsala, Sweden) or Anton Paar Monowave 200 instrument (Anton Paar GmbH, Graz, Austria).

Automated C18 column flash chromatography was run on a Flash Master Solo with an Argonaut UV-Vis detector from Omnialab and a Gilson FC 204 fraction collector. Separations were achieved by using C18 silica gel from Supelco packed into an ISOLUTE reservoir (70 mL) from Biotage. Flash column solvents were bidistilled water (solvent A) and MeOH (solvent B). Applied flash column gradient: 0–10 min: 90% A, 10% B; 10–70 min: linear gradient from 90% A, 10% B to 0% A, 100% B; 70–90 min: 0% A, 100% B. The flow rate was $2.0 \text{ mL}\cdot\text{min}^{-1}$. Detection was performed at 220 to 240 nm. ICP-MS measurements were performed on an Agilent QQQ 8800 Triple quad spectrometer (Agilent Technologies, Santa Carla, USA), equipped with standard x-lens settings, nickel cones, and a “micro-mist” quartz nebulizer. All solutions were prepared from 60% HNO_3 (Merck 1.1518.500 ultrapure) and 18.2 M Ω Millipore water (Merck KGaA, Darmstadt, Germany). Re (Merck 1.70344.0100 H_2O) was measured against a series of dilutions of single element standards (0–250 ng/mL).

Crystallographic data were collected at 183(2) K on a Rigaku OD XtaLAB Synergy Dualflex diffractometer (Rigaku Europe SE, Neu-Isenburg, Germany) equipped with a Pilatus 200 K detector and a PhotonJet Cu K α source ($\lambda = 1.54184 \text{ \AA}$) or Mo K α source ($\lambda = 0.71073 \text{ \AA}$). Suitable crystals were covered with oil (Infineum V8512, formerly known as Paratone N), placed on a nylon loop that was mounted in CrystalCap Magnetic™ (Hampton Research), and immediately transferred to the diffractometer. The program suite CrysAlis^{Pro} was used for data collection, multi-scan absorption correction, and data reduction [64]. The structures were solved with direct methods using SHELXS-97 [65] and were refined by full-matrix least squares methods on F^2 with SHELXL-2014 [66]. The GUI ShelXle was employed [67].

For NMR, ICP-MS, and (HR)-ESI-MS measurements of functionalized silica particles, a precise amount of these particles (typically 5–10 mg) were decomposed at room temperature for 1–20 h in 1 M NaOD in D_2O (typically 0.7 mL) for NMR or 1M NaOH (typically 0.7 mL) for MS.

Detailed synthetic procedures for all reported reactions as well as control reactions are described in the supplementary information.

3.1. Synthesis of **1d**

The 2-quinolinecarboxaldehyde (825 mg, 5.25 mmol) was dissolved in 1,2-dichloroethane (28 mL) and 4-aminobutyric acid (258 mg, 2.50 mmol) was added and stirred for 2 h at room temperature. Sodium triacetoxyborohydride (1.219 g, 5.75 mmol) was added and the solution was stirred at r.t. for 3 h. The 1,2-dichloroethane was evaporated in vacuo, the crude product was redissolved in dichloromethane (25 mL), and washed with H_2O ($3 \times 25 \text{ mL}$). The organic phase was dried in vacuo and purified by flash chromatography over C-18 silica, resulting in **1d** (277 mg, 0.719 mmol, 29%).

HR-MS (ESI): calcd. for $[\text{C}_{24}\text{H}_{23}\text{N}_3\text{O}_2+\text{H}]^+$: 386.18630, found: 386.18664. ^1H -NMR (400 MHz, CDCl_3) δ = 8.08–8.06 (m, 4H), 7.73 (d, J = 8.1 Hz, 2H), 7.68–7.61 (m, 4H), 7.48 (t, J = 7.5 Hz, 2H), 4.05 (s, 4H), 2.75 (t, J = 6.1 Hz, 2H), 2.37 (t, J = 6.6 Hz, 2H), 1.95–1.89 (m, 2H). ^{13}C NMR (126 MHz, CDCl_3) δ = 177.13, 159.22, 147.41, 136.98, 129.78, 128.75, 127.67, 127.49, 126.53, 121.53, 60.84, 54.82, 34.20, 22.54.

IR: 3061w, 2946w, 2814w, 1957w, 1701m, 1620w, 1598m, 1564w, 1504m, 1428m, 1308w, 1240m, 1112m, 907w, 826s, 732s.

3.2. Synthesis of 2

The **1d** (28 mg, 0.07 mmol), 3-aminopropyltriethoxysilane (17.7 mg, 18.7 μ L, 0.08 mmol) and hexafluorophosphate benzotriazole tetramethyl uronium (82.6 mg, 0.22 mmol) were dissolved in dry DMF (3 mL) and *N,N*-diisopropylethylamine (28 mg, 37.24 μ L, 0.22 mmol) was added. The mixture was stirred at r.t. for 2 h. The organic phase was washed with H₂O (3 \times 10 mL), filtered, and the DMF was evaporated under reduced pressure to yield **2** (35 mg, 0.06 mmol, 85%).

HR-MS (ESI:) calcd. for [C₃₃H₄₅N₄O₄Si+H]⁺: 589.32119, found: 589.32046. ¹H-NMR (400 MHz, CDCl₃) δ = 8.08 (d, *J* = 8.5 Hz, 2H), 8.04 (d, *J* = 8.4 Hz, 2H), 7.77 (d, *J* = 8.1 Hz, 2H), 7.68 (t, *J* = 7.6 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.50 (t, *J* = 7.5 Hz, 2H), 4.01 (s, 4H), 3.77 (q, *J* = 7.0 Hz, 6H), 3.10 (q, *J* = 6.6 Hz, 2H), 2.68 (t, *J* = 6.8 Hz, 2H), 2.17 (t, *J* = 7.4 Hz, 2H), 1.95–1.88 (m, 2H), 1.56–1.48 (m, 2H), 1.19 (t, *J* = 7.0 Hz, 9H), 0.56–0.52 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ = 172.88, 160.55, 147.69, 136.40, 129.56, 129.12, 127.65, 127.45, 126.31, 121.41, 61.52, 58.56, 54.35, 41.97, 34.66, 23.81, 23.06, 18.42, 7.90.

3.3. Synthesis of 3

The 2-quinolinecarboxaldehyde (128 mg, 0.81 mmol) was dissolved in 1,2-dichloroethane (20 mL) and 3-aminopropyltriethoxysilane (87 mg, 92 μ L, 0.40 mmol) was added. The mixture was stirred at 25 °C for 2 h, sodium triacetoxyborohydride (252 mg, 1.18 mmol) was added, and the mixture was stirred for 3.5 h at 25 °C. The 1,2-dichloroethane was evaporated in vacuo, EtOH (15 mL) was added, and stirred for 10 min at 25 °C. The EtOH was evaporated in vacuo. The residue was washed with toluene (20 mL) and the yellow solution was separated from the white precipitate by centrifugation. The toluene was evaporated to yield crude **3**. The product was purified by flash chromatography over C-18 silica, leading to the isolation of **3** (99 mg, 0.197 mmol, 49%).

HR-MS (ESI:) calcd. for [C₂₉H₃₇N₃O₃Si+H]⁺: 504.26770, found: 504.26794. ¹H-NMR (400 MHz, CDCl₃) δ = 8.11 (d, *J* = 8.5 Hz, 2H), 8.04 (d, *J* = 8.5 Hz, 2H), 7.78–7.74 (m, 4H), 7.67 (t, *J* = 7.6 Hz, 2H), 7.49 (t, *J* = 7.4 Hz, 2H), 4.02 (s, 4H), 3.72 (q, *J* = 7.0 Hz, 4H), 2.63 (t, *J* = 7.3 Hz, 2H), 1.72–1.64 (m, 2H), 1.14 (t, *J* = 7.0 Hz, 9H), 0.58–0.54 (m, 2H). ¹³C-NMR (126 MHz, CDCl₃) δ = 161.0, 147.7, 136.4, 129.5, 129.2, 127.6, 127.5, 126.2, 121.2, 61.7, 58.5, 58.0, 20.8, 18.4, 8.1. ²⁹Si-NMR (99.36 MHz, CDCl₃): δ = −45.01 ppm. IR: 2975w, 2928w, 2881w, 1600m, 1506m, 1429w, 1390w, 1313w, 1164w, 1100s, 1074s, 950m, 831m, 767s.

3.4. General Procedure for the Synthesis of {Re(CO)₃}⁺ Complexes

Between 0.15 and 0.01 mmol of the ligands (**1a**, **1b**, **1e**, and **3**) were dissolved in 1 to 5 mL MeOH ([**(3)Re(CO)₃**]⁺ = EtOH) and equimolar amounts of (NEt₄)₂[ReBr₃(CO)₃] were added. A microwave vial containing the reaction solution was purged with N₂ for 5 min. The mixture was heated to 85 °C (110 °C for [**(1e)Re(CO)₃**]⁺ and [**(3)Re(CO)₃**]⁺) for 45 min in a microwave reactor. H₂O was added to the vial and the formed precipitate was removed by filtration or centrifugation. From the clear solution, the product was precipitated by the addition of NH₄PF₆ as the corresponding PF₆ salt and collected by filtration or centrifugation. The [**(3)Re(CO)₃**](PF₆) was directly precipitated from the aqueous solution by the addition of NH₄PF₆. The products were washed with several mL of H₂O and dried under high vacuum.

3.4.1. Analytical Data for [(**1a**)Re(CO)₃](PF₆)

HR-MS (ESI:) calcd. for [C₂₆H₂₁N₃O₃Re]⁺: 610.11349, found: 610.11355. ¹H-NMR (500 MHz, CDCl₃) δ = 8.48 (d, *J* = 8.8 Hz, 2H), 8.36 (d, *J* = 8.4 Hz, 2H), 7.90 (d, *J* = 8.0 Hz, 2H), 7.84 (t, *J* = 7.5 Hz, 2H), 7.66 (m, 4H), 6.31 (m, 1H), 5.77 (d, *J* = 16.8 Hz, 1H), 5.69 (d, *J* = 10.2 Hz, 1H), 5.08 (m, 4H), 4.32 (d, *J* = 7.1 Hz, 2H). ¹³C-NMR (125 MHz, CDCl₃) δ = 195.62, 194.14, 164.48, 147.11, 141.89, 133.24, 129.82, 129.59, 128.58, 128.54, 128.43, 127.34, 120.17, 70.42, 68.85. IR: 2026s (CO), 1903s (CO), 1712w, 1604w, 1516w, 1432w, 1369w, 1291w, 1217w, 1149w, 1124w, 948w, 835s 747w.

Crystals suitable for X-ray diffraction analysis were obtained by vapor diffusion of cyclohexane into a THF solution of [(1a)Re(CO)₃](PF₆).

3.4.2. Analytical Data for [(1b)Re(CO)₃](PF₆)

HR-MS (ESI:) calcd. for [C₂₉H₂₇N₃O₅Re]⁺: 684.15027, found: 684.14980. ¹H-NMR (400 MHz, CDCl₃) δ = 8.49 (d, *J* = 8.7 Hz, 2H), 8.34 (d, *J* = 8.4 Hz, 2H), 7.91 (dd, *J* = 3.1 Hz, 2H), 7.85–7.81 (m, 2H), 7.66 (t, *J* = 7.2 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 5.25–5.13 (m, 4H), 4.48 (s, 2H), 1.45 (s, 9H). ¹³C-NMR (125 MHz, CDCl₃) δ = 195.54, 193.76, 166.65, 164.76, 147.02, 141.62, 133.15, 129.81, 128.59, 128.52, 128.30, 119.74, 84.83, 70.40, 66.83, 28.09. IR: 2159w, 2027s (CO), 1910s (CO), 1735w, 1519w, 1370w, 1243w, 1160m, 1034w, 844s, 780w.

Crystals suitable for X-ray diffraction analysis were obtained by vapor diffusion of cyclohexane into a THF solution of [(1b)Re(CO)₃](PF₆).

3.4.3. Analytical Data for [(1e)Re(CO)₃](PF₆)

HR-MS (ESI:) calcd. for [C₂₆H₂₂N₃O₄Re]⁺: 628.12406, found: 628.12394. ¹H-NMR (400 MHz, CDCl₃) δ = 8.47 (d, *J* = 3.1 Hz, 2H), 8.35 (d, *J* = 8.3 Hz, 2H), 7.89 (d, *J* = 3.2 Hz, 2H), 7.85–7.81 (m, 2H), 7.68–7.63 (m, 4H), 5.16–5.04 (m, 4H), 3.99–3.95 (m, 2H), 3.84 (t, *J* = 5.6 Hz, 2H), 2.30–2.23 (m, 2H). ¹³C-NMR (126 MHz, CDCl₃) δ = 195.72, 194.15, 164.64, 147.10, 141.87, 133.21, 129.78, 128.59, 128.55, 128.43, 120.21, 68.70, 65.93, 59.80, 29.23. IR: 3617w, 2919w, 2025s (CO), 1932m (CO), 1897s (CO) 1597w, 1519w, 1435w, 1371w, 1306w, 1214w, 1126w, 1047w, 831s, 742m, 659m.

Crystals suitable for X-ray diffraction analysis were obtained by vapor diffusion of cyclohexane into a THF solution of [(1e)Re(CO)₃](PF₆).

3.4.4. Analytical Data for [3-Re](PF₆)

HR-MS (ESI:) calcd. for [C₃₂H₃₇N₃O₆ReSi]⁺: 774.20036, found: 774.20035. ¹H-NMR (500 MHz, CDCl₃) δ = 8.46 (d, *J* = 8.8 Hz, 2H), 8.33 (d, *J* = 8.5 Hz, 2H), 7.88 (d, *J* = 8.0 Hz, 2H), 7.83–7.80 (m, 2H), 7.66–7.63 (m, 4H), 5.19–4.96 (m, 4H), 3.84 (q, *J* = 7.0 Hz, 6H), 2.16–2.10 (m, 2H), 1.58 (s, 2H), 1.20 (t, *J* = 7.0 Hz, 9H), 0.75 (t, *J* = 7.7 Hz, 2H). ¹³C-NMR (126 MHz, CDCl₃) δ = 195.8, 194.2, 164.7, 147.1, 141.8, 133.1, 129.8, 128.6, 128.5, 128.4, 120.3, 70.7, 68.7, 58.8, 20.4, 18.4, 7.7. ²⁹Si-NMR (99.38 MHz, CDCl₃): δ = −47.44 ppm. IR: 2976w, 2891w, 2025s (CO), 1901s (CO), 1602w, 1517w, 1470w, 1436w, 1394w, 1300w, 1205w, 1163w, 1074m, 958w, 873w, 835s, 779m, 749m, 647w. UV-Vis (CHCl₃, 10^{−5} M): 323 nm (13696 M^{−1}·cm^{−1}). Fluorescence (CHCl₃, 10^{−5} M): λ_{ex} (326), λ_{em} air (426, 546), λ_{em} N₂ (383, 566).

3.5. Synthesis of 3@SBA-15

SBA-15 particles (213 mg) were dried by heating (140 °C) under high vacuum for 4 h. Then, 3 (10 mg, 0.02 mmol) was dissolved in dry toluene (5 mL) and added to the SBA-15 particles. The suspension was sonicated at 60 °C for 2 h. Filtration, washing with toluene (5 mL) and Et₂O (5 mL), and drying under high vacuum led to the isolation of 3@SBA-15 (176 mg).

EA: C 2.46, H 0.49, N 0.32. HR-ESI of dissolved particles (1M NaOD in D₂O): calc. for [C₂₃H₂₅O₃N₃Si+H]⁺: 420.17379, found: 420.17345. ¹H-NMR (1M NaOD in D₂O 500 MHz): δ = 7.76 (d, *J* = 8.5 Hz, 2H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.52–7.49 (m, 4H), 7.34 (t, *J* = 7.0 Hz, 2H), 7.24 (d, *J* = 8.5 Hz, 2H), 3.88 (s, 4H), 2.70 (t, *J* = 7.8 Hz, 2H), 1.72–1.69 (m, 2H), 0.38 (t, *J* = 8.4 Hz, 2H).

3.6. Synthesis of 3-Re@SBA-15

3.6.1. Method A: Grafting of 3-Re onto SBA15

SBA-15 particles were dried by heating (140 °C) under high vacuum for 4 h. The dry SBA-15 particles (200 mg) were dispersed in dry DCM (5 mL). The suspension was transferred into a microwave vial and [3-Re](PF₆) (9.2 mg, 0.01 mmol) was added. The suspension was sonicated for 2 h at 60 °C.

After filtration, washing with DCM (3 mL), and drying under high vacuum, **3-Re@SBA-15** (202 mg) was isolated.

EA: Found: C 2.70, H 0.57, N 0.21. IR: 2026w (CO), 1901w (CO), 1891w (CO), 1631w, 1053s (Si–O), 964m, 818w, 649w.

3.6.2. Method B: Reaction of $(\text{NEt}_4)_2[\text{Re}(\text{H}_2\text{O})_3(\text{CO})_3]$ with **3@SBA-15**

$(\text{NEt}_4)_2[\text{Re}(\text{CO})_3\text{Br}_3]$ (38.4 mg, 0.050 mmol) was dissolved in H_2O (6 mL) and AgNO_3 (25.2 mg, 0.148 mmol) was added. The solution turned milky and a precipitate was formed immediately. After stirring for 60 min at r.t. the precipitate was filtered. A clear solution $[\text{Re}(\text{H}_2\text{O})_3(\text{CO})_3]\text{NO}_3$ was obtained (pH 6–7). This solution was added to **3@SBA-15** (80 mg) particles and the suspension was heated at 100 °C for 45 min in a microwave reactor. Finally, **3-Re@SBA-15** (71 mg) was isolated by filtration, washed with H_2O (2 mL) and toluene (4 mL), and dried under vacuum.

EA: C: 2.28 H: 0.80 N: 0.30. Nitrogen sorption: BET: 217 m^2/g ; average pore size: 7.0 nm; total pore volume: 0.43 cm^3/g . IR: 2026w (CO), 1901w (CO), 1891w (CO), 1631w, 1053s (Si–O), 964 m, 818w, 649w. ICP-MS: 1.4% w; 0.077 mmol/g particles; 0.07 Re atoms/ nm^2 .

3.7. Synthesis of Bifunctionalized Mesoporous Silica Particles (**EOITC/3@SiP**)

Silica particles (SiP = SBA-15, spherical sSBA-15) were dried by heating (140 °C) under high vacuum for 4 h, then dispersed in hexane, and 3-aminopropyltris(methoxyethoxyethoxy)silane (APTMEES) was added. The suspension was sonicated for 10 min at room temperature. The particles were recovered by filtration, washed with hexane (3×3 mL), and dried under high vacuum, yielding **APTMEES@SiP**. Eosin isothiocyanate (EOITC) was dissolved in EtOH (10 mL). **APTMEES@SiP** particles were added and the suspension was stirred at r.t. for 16 h. The particles were collected by filtration, washed with EtOH (50 mL) and H_2O (50 mL), yielding **EOITC/@SiP**. Then, **3** was dissolved in dry toluene and added to dry **EOITC/@SiP** particles. The suspension was sonicated at 40 °C for 2 h. Finally, **EOITC/3@SiP** was filtered off, washed with toluene (5 mL) and Et_2O (5 mL), and dried under high vacuum.

3.8. Reaction of Bifunctionalized Mesoporous Silica Particles (**SiP**) with $[\text{Re}(\text{H}_2\text{O})_3(\text{CO})_3]^+$

The $(\text{NEt}_4)_2[\text{Re}(\text{CO})_3\text{Br}_3]$ was dissolved in H_2O and 3 equiv AgNO_3 were added. A colorless precipitate was formed immediately. After stirring for 60 min at r.t. the precipitate was filtered off. A clear solution of $[\text{Re}(\text{H}_2\text{O})_3(\text{CO})_3]\text{NO}_3$ was obtained (pH 6–7). This solution was added to the **EOITC/3@SiP** (SiP = SBA-15, spherical sSBA-15) and the suspension was heated at 100 °C for 45 min by means of a microwave reactor. The formed **EOITC/3-Re@SiP** particles were collected by filtration, washed with H_2O (2 mL) and toluene (4 mL), and dried under vacuum.

3.9. Labeling of Bifunctionalized Mesoporous Silica Particles (**SiP**) with $[\text{}^{99\text{m}}\text{Tc}(\text{H}_2\text{O})_3(\text{CO})_3]^+$

A microwave vial was charged with **EOITC/3@SiP** (SiP = SBA-15, sSBA-15) (10 mg) and saline (2 mL). The vial was flushed with N_2 (5 min). The $[\text{}^{99\text{m}}\text{Tc}(\text{H}_2\text{O})_3(\text{CO})_3]^+$ (5–15 MBq) in saline (2 mL, pH 7) was added and the suspension was heated at 100 °C for 15 min in the microwave reactor. For reaction control, an aliquot (0.5 mL) was filtered and centrifuged, and the clear solution was used for radio-HPLC measurements. As an additional control, 10 μL of each centrifuged sample was collected and the remaining activity in solution was determined by means of a γ -counter.

4. Conclusions

We combined the multimodal properties of the bisquinoline/ $[\text{M}(\text{CO})_3]^+$ system ($\text{M} = \text{}^{99\text{m}}\text{Tc}$, Re) with the theranostic properties of the $\text{}^{99\text{m}}\text{Tc}/^{186/188}\text{Re}$ pair at a mesoporous silica support. The presented synthetic procedures are based on fundamental studies, which disclosed the most suitable mesoporous silica construct (SBA-15) for this development. Furthermore, a variety of different pathways was developed to synthesize bisquinoline-containing silanes, suitable for grafting reactions with silica

particles. The hydrolysis of the trialkoxysilane moiety and subsequent cross-linking of the products had to be addressed. The successful functionalization of the external and the pore surface of the mesoporous silica particles was visualized by confocal laser scanning microscopy. The synthesized model system mimics a SBA-15-based target-specific theranostic nanoplatform, which enables the combination of fluorescence and radio imaging with the possibility of radio- and chemotherapy. Currently, we are using the reported procedures to synthesize target-specific nanoparticles for the first in vitro and in vivo studies.

Supplementary Materials: The following are available online at <http://www.mdpi.com/2304-6740/7/11/134/s1>, Figure S3.2.1: Experimental Setup to distinguish the labeling performance of different NorboSi modified silica particles, Figure S3.2.2: Labeling performance of different NorboSi modified silica particles with $[^{99m}\text{TcO}_3(\text{tacn})]\text{Cl}$, Figure S4.2.4.1: IR spectrum of **3-Re**(PF₆), Figure S4.4.2.1: HPLC traces of the labeling of **3@SBA-15** with $[^{99m}\text{Tc}(\text{H}_2\text{O})_3(\text{CO})_3]^+$, Figure S4.4.2.2: Control reaction of SBA-15 with $[^{99m}\text{Tc}(\text{H}_2\text{O})_3(\text{CO})_3]^+$, Figure S5.1.1: ^1H -NMR of **1a** in CDCl₃, Figure S5.1.2: ^{13}C -NMR of **1a** in CDCl₃, Figure S5.2.1: ^1H -NMR of **1b** in CDCl₃, Figure S5.2.2: ^{13}C -NMR of **1b** in CDCl₃, Figure S5.3.1: ^1H -NMR of **1c** in CDCl₃, Figure S5.3.2: ^{13}C -NMR of **1c** in MeOD, Figure S5.3.3: ^{19}F -NMR of **1c**, Figure S5.4.1: ^1H -NMR of **1d** in CDCl₃, Figure S5.4.2: ^{13}C -NMR of **1d** in CDCl₃, Figure S5.5.1: ^1H -NMR of **1e** in CDCl₃, Figure S5.5.2: ^{13}C -NMR of **1e** in CDCl₃, Figure S5.6.1: ^1H -NMR of **2** in CDCl₃, Figure S5.6.2: ^{13}C -NMR of **2** in CDCl₃, Figure S5.7.1: ^1H -NMR of **3** in CDCl₃, Figure S5.7.2: ^{13}C -NMR of **3** in CDCl₃, Figure S5.7.3: ^1H -NMR of **3-OD** in MeOD/1M NaOD in D₂O with a ratio of 1:3, Figure S5.8.1: ^1H -NMR of **[(1a)Re(CO)₃](PF₆)** in CDCl₃, Figure S5.8.2: ^{13}C -NMR of **[(1a)Re(CO)₃](PF₆)** in CDCl₃, Figure S5.9.1: ^1H -NMR of **[(1b)Re(CO)₃](PF₆)** in CDCl₃, Figure S5.9.2: ^{13}C -NMR of **[(1b)Re(CO)₃](PF₆)** in CDCl₃, Figure S5.10.1: ^1H -NMR of **[(1e)Re(CO)₃](PF₆)** in CDCl₃, Figure S5.10.2: ^{13}C -NMR of **[(1e)Re(CO)₃](PF₆)** in CDCl₃, Figure S5.11.1: ^1H -NMR of **3-Re** in CDCl₃, Figure S5.11.2: ^{13}C -NMR of **3-Re** in CDCl₃, Figure S5.11.3: ^1H -NMR of **3@SBA** in 1M NaOD in D₂O, Table S1: Characteristics of silica particles applied in this study, Table S2: Analytical data for NorboSi@SBA-15, Crystallographic data of **1c**, **[(1a)Re(CO)₃](PF₆)**, **[(1b)Re(CO)₃](PF₆)**, **[(1e)Re(CO)₃](PF₆)**. The CIF and the checkCIF output files are included in the Supplementary Materials.

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Towards ^{99m}Tc - and Re-Based Multifunctional Silica Platforms for Theranostic Applications

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Supplementary Information

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1. Materials

Caution: ^{99m}Tc is a γ -emitter. All experiments have to be performed in laboratories approved for working with low-level radioactive materials.

All chemicals were of reagent-grade quality or higher and were obtained from commercial suppliers. Solvents were used as received or dried over molecular sieves. $\text{Na}[^{99m}\text{TcO}_4]$ in 0.9% saline was eluted from a $^{99}\text{Mo}/^{99m}\text{Tc}$ UTK FM generator purchased from Mallinckrodt Medical B.V. (The Netherlands). $[^{99m}\text{Tc}(\text{CO})_3(\text{H}_2\text{O})_3]^+$ was synthesized according to an adapted version of a published procedure.[1] The $[^{99m}\text{TcO}_3(\text{tacz})]^+$ was synthesized according a literature procedure.[2] Purity of all ^{99m}Tc complexes was controlled by HPLC analysis.

Silica particles used in this study are MCM-41 with various pore sizes, SBA-15, spherical SBA-15 (sSBA-15), hexagonal arrays of silica nanochannels (ASNCs), and MCM-41 nanoparticles. The particles were synthesized following literature procedures (sSBA-15,[3] ASNCs,[4] all others[5]). Characteristics of the applied silica particles are summarized in table S1.

Table S1: Characteristics of silica particles applied in this study.

Particles	Shape	Particle Size [μm]	BET-Surface Area [m^2/g]	Total Pore Volume [cm^3/g]	Average Pore Diameter [nm]	External Surface Area [% of total surface area]
SBA-15	irregular	1-2	700	0.90	7.3	6
sSBA-15	spherical	5	800	0.66	4.9 (broad)	-
MCM-41	irregular	1-2	870	0.74	3.9	8
MCM-41-C12	irregular	1-2	668	0.46	2.8	5
MCM-41-C10	irregular	1-2	608	0.33	2.5	-
MCM-41-nano	spherical	0.02-0.05	702	0.98	3.3	60
ASNCs_short	hexagonal prismatic	2 x 2	1254	0.76	3.2	6
ASNCs_long	hexagonal prismatic	2 x 5	1200	0.84	3.4	3

2. Characterization

High-resolution mass spectrometry (HR-ESI-MS) was performed on a Bruker maXis QToF high-resolution mass spectrometer (Bruker GmbH, Bremen, Germany).

^1H and ^{13}C -NMR spectra were recorded in deuterated solvents on a Bruker AV-400 or Bruker AV-500 MHz spectrometer at 300 K. ^{13}C -NMR spectra were proton decoupled. The chemical shifts (δ) are reported in ppm relative to residual solvent peaks (dmf- d_7 ^1H : 8.03 ppm, ^{13}C : 163.15 ppm; CDCl_3 : ^1H : 7.26 ppm, ^{13}C : 77.16 ppm; MeOD: ^1H : 3.31 ppm, ^{13}C : 49.00 ppm; Acetone- d_6 : ^1H : 2.05 ppm, ^{13}C : 29.84 ppm). The abbreviations for the peak multiplicities are as follows: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet), br (broad). ^{29}Si -NMR spectra were recorded on a Bruker AV-500 MHz.

Gamma-counting of the $^{99\text{m}}\text{Tc}$ solutions was performed on a COBRA 5002 (Packard). Half-life time corrections for the labeling of silica particles were neglected due to the sequential measurement of the samples with less than 5 min between two samples. Labeling of silica particles: The initial activity of the $^{99\text{m}}\text{Tc}$ -solutions was determined prior to the addition of the particle-suspension. According to the dilution (factor 2), the activity for $t = 0$ min was calculated.

HPLC analyses were performed on a Merck Hitachi LaChrom L 7100 pump coupled to a Merck Hitachi LaChrom L7200 tunable UV detector and a radiodetector. UV-Vis detection was performed at 250 nm. The detection of radioactive $^{99\text{m}}\text{Tc}$ complexes was performed with a Berthold LB508 radiodetector equipped with BGO cell. Separations were achieved on a Macherey-Nagel C18 reversed-phase column (Nucleosil 10 μm , 250 \times 4 mm) using a gradient of methanol (solvent A) and 0.1% trifluoroacetic acid (solvent B). Applied HPLC gradient: 0–3 min: 0% A, 100% B; 3–3.1 min: 0–25% A, 100–75% B; 3.1–9 min: 25% A, 75% B; 9–9.1 min: 25–34% A, 75–66% B; 9.1–18 min: 34–100% A, 66–0% B; 18–25 min: 100% A, 0% B; 25–25.1 min: 100–0% A, 0–100% B; 25.1–30 min: 0% A, 100% B. The flow rate was 0.5 ml min^{-1} . UPLC-ESI-MS was performed on a Waters Acquity UPLC System coupled to a Bruker HCTM, using an Acquity UPLC BEH C18 1.7 μm (2.1 \times 50 mm) column. UPLC solvents were formic acid (0.1% in millipore water) (solvent A) and acetonitrile HPLC grade (solvent B). Applied UPLC gradient: 0–0.5 minutes: 95% A, 5% B; 0.51–4.0 minutes: linear gradient from 95% A (5% B) to 0% A (100% B); 4–5 minutes: 100% B. The flow rate was 0.6 ml/min . Detection was performed at 250 nm and 480 nm (DAD). For preparative HPLC a Varian ProStar 320 system was used with a Dr. Maisch Reprosil C18 100-7 (40 \times 250 mm) column. The solvents (HPLC grade) were 0.1% trifluoroacetic acid (solvent A) and acetonitrile (solvent B). Applied HPLC gradient: 0–2 minutes: 66% A (34% B); 2–45 minutes: linear gradient from 66% A (34% B) to 0% A (100% B); 45–51 minutes: 100% B. The flow rate was 40 mL/min . Detection was performed at 235 nm.

IR-Spectra were recorded on a Perkin-Elmer FT-IR Spectrum Two spectrometer, using ATR technique and applied as neat samples.

Nitrogen sorption isotherms were collected at 77 K using a Quantachrome NOVA 3000. Samples were vacuum-degassed at 80 $^\circ\text{C}$ for 3 h. The total surface area was calculated by the Brunauer-Emmett-Teller (BET) method. Mesopore size distributions were evaluated by the nonlocal density functional theory (NLDFIT) method developed for silica exhibiting cylindrical pore geometry (NOVAWin software, Version 11.0, Quantachrome Instruments). The adsorption branch of the respective isotherm was used for the calculations.

The fluorescence and CLSM setup consisted of an Olympus BX60 microscope equipped with a FluoView FV300 confocal unit and lasers operating at 488 and 543.5 nm. Optical slices in the center of the particles were selected.

UV-Vis spectra were measured with a Cary 50 UV/Vis spectrometer or a SPECORD® 250 PLUS spectrometer (Analytik Jena) with solution samples in 1 cm quartz cells.; λ_{max} (ϵ) in nm; ϵ in $\text{M}^{-1} \text{cm}^{-1}$. Fluorescence Spectra were recorded with a LS 50 B Luminescence Spectrometer (Perkin Elmer); λ_{em}

(λ_{ex}) in nm. Lifetime and transient absorption measurements were recorded on a LP920-K laser flash photolysis transient absorption spectrometer using a flash lamp pumped Q-switched Nd:YAG laser (355 nm) as excitation source. Probing of the sample was conducted by a Xe920 probe lamp (450 W) and an xP920 pulsing unit module. Argon-purged solution samples in 1 cm quartz-cells were used.

Microwave reactions were performed with a Biotage Initiator+ Robot Eight (BI) or Anton Paar (AP) Monowave 200 instrument.

Automated-C18-Column flash chromatography was run on a Flash Master Solo with an Argonaut UV-Vis detector from Omnilab and a Gilson FC 204 fraction collector. Separations were achieved by use of C18 silica gel from Supelco packed into a ISOLUTE reservoir (70ml) from Biotage. Flash column solvents were bidistilled water (solvent A) and MeOH (solvent B). Applied flash column gradient: 0–10 min: 90% A, 10 % B; 10–70 min: linear gradient from 90% A, 10% B to 0% A, 100% B; 70-90 min: 0% A, 100% B. The flow rate was 2.0 mL min⁻¹. Detection was performed at 220 to 240 nm.

ICP-MS measurements were performed on an Agilent QQQ 8800 Triple quad spectrometer, equipped with standard x-lens setting, nickel cones and a “micro-mist” quartz nebulizer. All solutions were prepared from 60% HNO₃ (Merck 1.1518.500 ultrapur) and 18.2 MΩ Millipore water. Re (Merck 1.70344.0100 H₂O) was measured against a series of dilutions of single element standards (0 – 250 ng/ml).

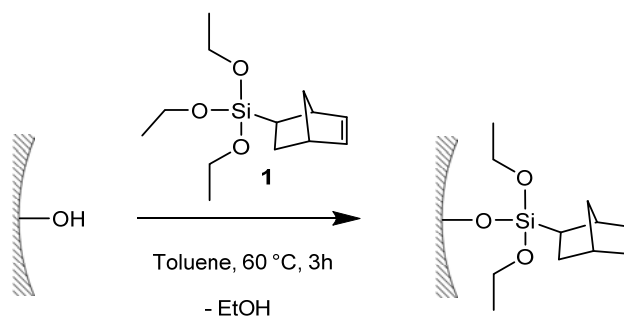
For NMR, ICP-MS and (HR)-ESI-MS measurements of functionalized silica particles a precise amount of these particles (typically 5-10 mg) were decomposed at r.t. for 1-20 h in 1M NaOD in D₂O (typically 0.7 ml) for NMR or 1M NaOH (typically 0.7 ml) for MS.

3. Comparison of the Labelling Performance of Functionalized Silica Microparticles

3.1 Grafting of Norbornenesilane onto Silica Particles

The commercially available 5-(bicycloheptenyl)triethoxysilane (NorboSi) was attached to the silica particles via postsynthetic modification (scheme S3.1.1).^[6]

Silica particles were dried by heating (140 °C) under high vacuum for 4 h. Silica particles, dry toluene (3 ml) and 5-(bicycloheptenyl)triethoxysilane (NorboSi) were sonicated at 60 °C for 3 h. The NorboSi modified silica particles were filtered, washed with toluene (2 ml) and Et₂O (2 ml) and dried under high vacuum. The successful attachment was confirmed by nitrogen sorption measurements and elemental analysis. Table S2 shows the data for the most relevant particle type NorboSi@SBA-15.



Scheme S3.1.1: Grafting of NorboSi onto silica particles.

Table S2: Analytical data for NorboSi@SBA-15.

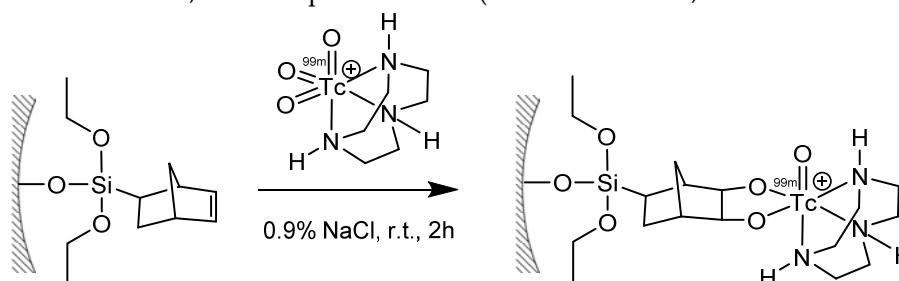
Particles	Silica particles [mg]	NorboSi [mmol]	BET-Surface Area [m ² /g]	Total Pore Volume [cm ³ /g]	Average Pore Size [nm]	EA [%]
SBA-15*	-		600	0.91	7.6	-
NorboSi@SBA-15	35	0.37	442	0.70	7.3	C 8.07
NorboSi@SBA-15	35	0.15	666	0.89	7.6	C 2.92

*Analytical data of the applied SBA-15 particles, before functionalization.

3.2 Labeling of NorboSi Modified Silica Particles with [^{99m}TcO₃(tacn)]Cl

[^{99m}TcO₃(tacn)]⁺ was synthesized, following published procedures.[2,6]

10 mg of NorboSi modified silica particles were suspended in 2 ml saline solution reacted with [^{99m}TcO₃(tacn)]⁺ in saline (2 ml, scheme S3.2.1). Sonication was used for the labeling with [^{99m}TcO₃(tacn)]⁺ in order to avoid agglomeration during the reaction. Standardized reaction conditions: sonication for 2h, start temperature 25°C (increased to 40°C, over the reaction time of 2h).



Scheme S3.2.1: Labeling of NorboSi modified silica particles with [^{99m}TcO₃(tacn)]Cl.

After 0,1, 5, 10, 15, 20, 25, 30, 40, 50, 60, 90 and 120 min aliquots (0.1 ml) were collected and centrifuged separately (5000 rpm) for 8 min. The clear solution was used for HPLC measurements and 10 µl of each centrifuged sample were collected and the remaining [^{99m}TcO₃(tacn)]Cl in solution was determined by the use of a γ-counter. Progress of labeling can be monitored by the decrease of the activity in solution over time (figure S3.2.1).

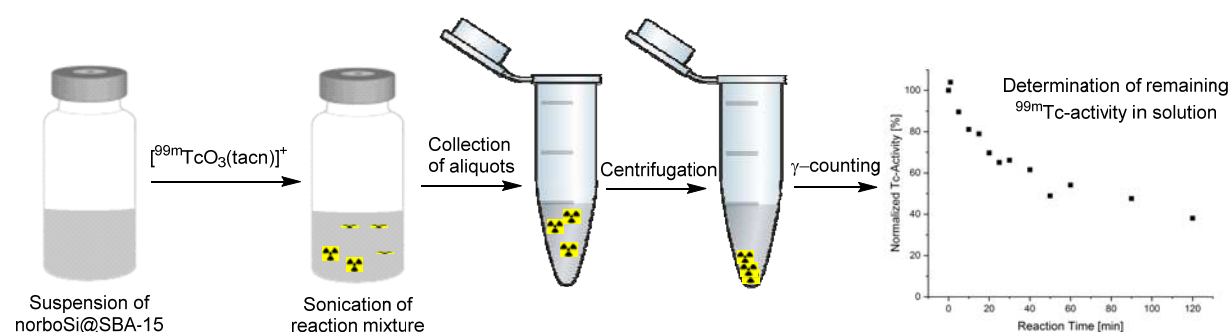


Figure S3.2.1: Experimental setup to distinguish the labeling performance of different NorboSi modified silica particles.

The results of this initial screening are summarized in figure S3.2.2.

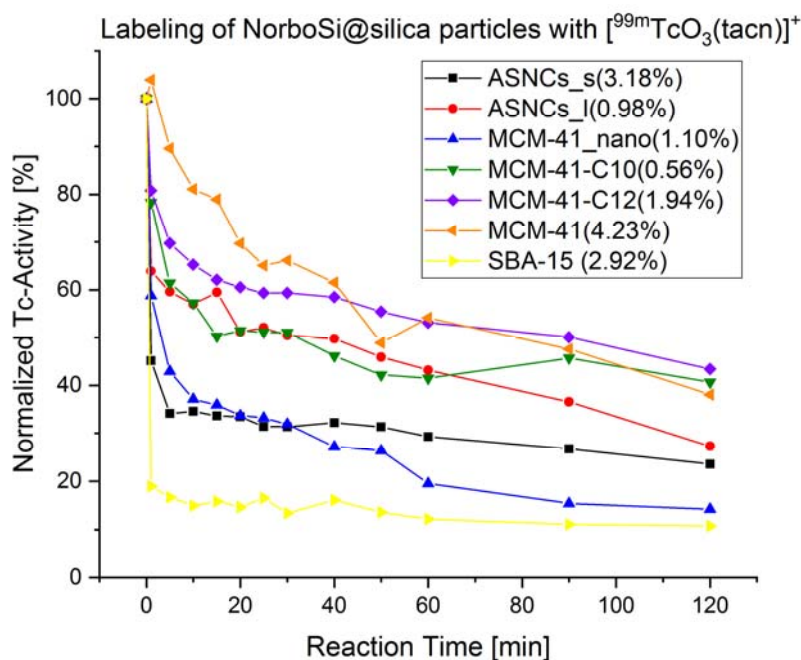


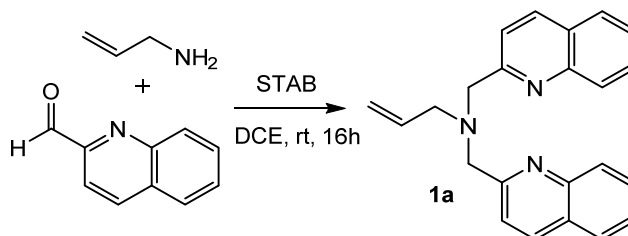
Figure S3.2.2: Labeling performance of different NorboSi modified silica particles with $[^{99m}\text{TcO}_3(\text{tacn})]\text{Cl}$. Numbers in brackets represent the carbon content of these particles, determined by elemental analysis.

Control reactions for the (3+2)-cycloaddition of $[^{99m}\text{TcO}_3(\text{tacn})]^+$ with NorboSi modified silica particles were published before and showed that $[^{99m}\text{TcO}_4]^-$ (starting compound for the $[^{99m}\text{TcO}_3(\text{tacn})]^+$ synthesis) and $[^{99m}\text{TcO}_3(\text{tacn})]^+$ did not show any reactions with unmodified silica particles. [6] A decrease of activity by 10% can be observed in the reaction of $[^{99m}\text{TcO}_3(\text{tacn})]^+$ with MCM-41. This can be explained by electrostatic adsorption of the $[^{99m}\text{TcO}_3(\text{tacn})]^+$ cation at the negatively charged MCM-41 surface (pH of the reaction solution = 7).

4. Synthetic Procedures and Experimental Data

4.1 Ligands and Silanes

4.1.1 Synthesis of 1a



2-quinolinecarboxaldehyde (345 mg, 2.195 mmol) was dissolved in 1,2-dichloroethane (DCE, 30 ml) and allylamine (59.7 mg, 78 μl , 1.045 mmol) was added. The reaction mixture was stirred for 30 min at r.t. under a N_2 atmosphere. Sodium triacetoxymethylborohydride (STAB, 665 mg, 3.136 mmol) was added and the solution was stirred at r.t. for 19 h. In this time the solution color turned from yellow to an intense orange. DCE was evaporated *in vacuo* and the crude product redissolved in MeOH (30 ml). After 10 min of stirring, the MeOH was evaporated. The crude orange solid was dissolved in DCM (30 ml), filtered and the DCM was evaporated *in vacuo*. Finally, the crude product was purified by column

chromatography (silica) with an eluent of MeOH:DCM 1:20. This led to the isolation of **1a** with a yield of 56% (199 mg, 0.586 mmol).

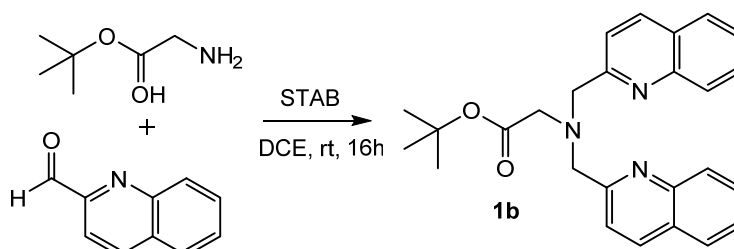
HR-MS (ESI): calcd. for $[C_{23}H_{21}N_3+H]^+$: 340.18132, found: 340.18082.

1H NMR (500 MHz, $CDCl_3$) δ = 8.11 (d, J = 8.5 Hz, 2H), 8.05 (d, J = 8.5 Hz, 2H), 7.75 (m, 4H), 7.67 (t, J = 7.5 Hz, 2H), 7.49 (t, J = 7.4 Hz, 2H), 5.98 (m, 1H), 5.28 (d, J = 17.1 Hz, 1H), 5.19 (d, J = 10.2 Hz, 1H), 4.05 (s, 4H), 3.28 (d, J = 6.0 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 160.41, 147.67, 136.51, 135.26, 129.51, 129.12, 127.62, 127.49, 126.27, 121.15, 118.57, 60.83, 57.67.

IR: 3057w, 2818w, 1603m, 1564w, 1504m, 1423m, 1359w, 1304m, 1231w, 1112m, 988m, 920m, 864m, 826s, 766s.

4.1.2 Synthesis of **1b**



2-quinolinecarboxaldehyde (165 mg, 1.05 mmol) was dissolved in 1,2-dichloroethane (DCE, 15ml) and glycine tert-butyl ester (65.6 mg, 68.3 μ l, 0.50 mmol) was added and stirred for 45 min at r.t. Sodium triacetoxyborohydride (STAB, 318 mg, 1.5 mmol) was added and the solution turned from pale yellow to orange. The solution was stirred at r.t. for 21 h. DCE was evaporated *in vacuo*, the crude product redissolved in MeOH (15 ml). After 10 min of stirring, the MeOH was evaporated. The crude orange solid was dissolved in DCM (30 ml), filtered and the DCM was evaporated *in vacuo*. Finally, the crude product was purified by column chromatography (silica) with an eluent of MeOH:DCM 1:20. This led to the isolation of **1b** with a yield of 34% (70 mg, 0.17 mmol).

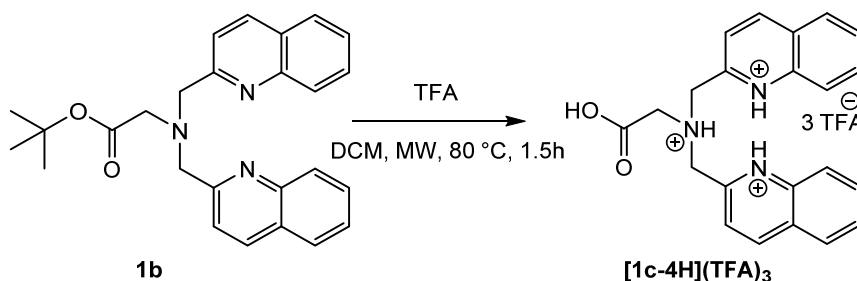
HR-MS (ESI): calcd. for $[C_{26}H_{27}N_3O_2+H]^+$: 414.21760, found: 414.21669.

1H NMR (400 MHz, $CDCl_3$) δ = 8.13 (d, J = 8.4 Hz, 2H), 8.05 (d, J = 8.5 Hz, 2H), 7.83 (d, J = 8.4 Hz, 2H), 7.79-7.77 (m, 2H), 7.70-7.66 (m, 2H), 7.52-7.48 (m, 2H), 4.15 (s, 4H), 3.41 (s, 2H), 1.45 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ = 170.52, 159.94, 147.56, 136.75, 129.57, 129.10, 127.68, 127.60, 126.38, 121.42, 61.06, 56.48, 53.56, 28.31.

IR: 2977w, 1730m, 1594w, 1501m, 1423w, 1370m, 1219w, 1141s, 980w, 829s, 751s.

4.1.3 Synthesis of **1c**



1b (41.35 mg, 0.1 mmol) was dissolved in DCM (4.5 ml). TFA (0.39 ml, 571 mg, 5.01 mmol) was added and the reaction mixture was heated to 90 $^{\circ}C$ for 20 min in a microwave reactor. DCM and remaining TFA were removed under reduced pressure and heating (1 mbar, 75 $^{\circ}C$). **[1c-4H](TFA)₃** was obtained with a yield of 59% (41 mg, 0.059 mmol).

MS (ESI) m/z = 358.2 $[M+H]^+$.

EA: Anal. calcd. for $C_{28}H_{22}F_9N_3O_8$: C 48.08, H 3.17, N 6.01; found: C 47.29, H 2.63, N 5.27.

1H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, J = 8.4 Hz, 2H), 8.45 (d, J = 8.7 Hz, 2H), 8.05 – 7.98 (m, 6H), 7.84 – 7.80 (m, 2H), 4.81 (s, 4H), 3.77 (s, 2H).

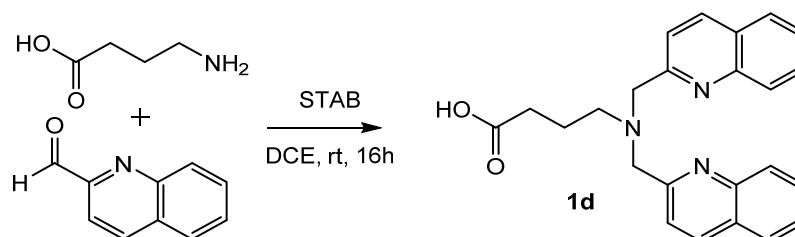
1H NMR (400 MHz, MeOD) δ = 9.09 (d, J = 8.6 Hz, 2H), 8.44 (d, J = 8.8 Hz, 2H), 8.28 (d, J = 8.3 Hz, 2H), 8.21 (d, J = 8.6 Hz, 2H), 8.17 (t, J = 7.8 Hz, 2H), 7.95 (t, J = 7.7 Hz, 2H), 4.84 (s, 4H), 3.94 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 173.71, 161.25 (q, J = 37.6 Hz, TFA-COOH), 156.82, 146.37, 138.71, 134.92, 129.90, 128.74, 128.17, 122.29, 121.33, 115.97 (q, J = 290.0 Hz, TFA- CF_3), 57.02, 56.39.

^{19}F NMR (376 MHz, $CDCl_3$) δ = -75.89

Crystals suitable for X-ray diffraction analysis were obtained by slow evaporation of a $CDCl_3$ solution of **1c**.

4.1.4 Synthesis of **1d**



2-quinolinecarboxaldehyde (825 mg, 5.25 mmol) was dissolved in 1,2-dichloroethane (DCE, 28 ml) and 4-aminobutyric acid (258 mg, 2.50 mmol) was added and stirred for 2 h at room temperature. Sodium triacetoxyborohydride (STAB, 1.219 g, 5.75 mmol) was added and the solution was stirred at r.t. for 3 h. DCE was evaporated *in vacuo*, the crude product redissolved in DCM (25 ml) and washed with H₂O (3 x 25 ml). The organic phase was dried *in vacuo* and purified by flash chromatography over C-18 silica, resulting in **1d** (277 mg, 0.719 mmol, 29%).

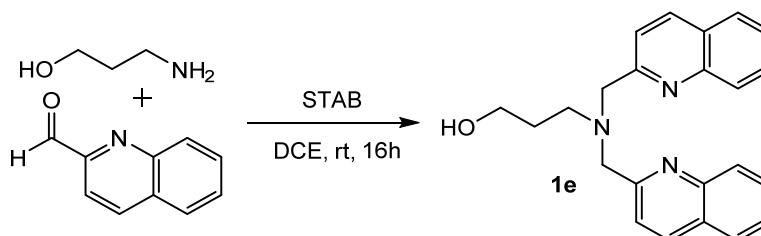
HR-MS (ESI): calcd. for $[C_{24}H_{23}N_3O_2+H]^+$: 386.18630, found: 386.18664.

1H NMR (400 MHz, $CDCl_3$) δ = 8.08-8.06 (m, 4H), 7.73 (d, J = 8.1 Hz, 2H), 7.68-7.61 (m, 4H), 7.48 (t, J = 7.5 Hz, 2H), 4.05 (s, 4H), 2.75 (t, J = 6.1 Hz, 2H), 2.37 (t, J = 6.6 Hz, 2H), 1.95-1.89 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ = 177.13, 159.22, 147.41, 136.98, 129.78, 128.75, 127.67, 127.49, 126.53, 121.53, 60.84, 54.82, 34.20, 22.54.

IR: 3061w, 2946w, 2814w, 1957w, 1701m, 1620w, 1598m, 1564w, 1504m, 1428m, 1308w, 1240m, 1112m, 907w, 826s, 732s.

4.1.5 Synthesis of **1e**



2-quinolinecarboxaldehyde (0.75 g, 4.77 mmol) was dissolved in 1,2-dichloroethane (DCE, 50 ml) and 3-amino-1-propanol (0.10 ml, 1.32 mmol) was added. After 1.5 h of stirring at r.t, sodium triacetoxyborohydride (STAB, 1.15 g, 5.43 mmol) was added and the solution was stirred at r.t. for 20 h. DCE was evaporated *in vacuo*, MeOH (25 ml) was added and the suspension filtered. MeOH was evaporated *in vacuo* and the residue was redissolved in DCM (35 ml). The formed white precipitate was removed by filtration and DCM was evaporated *in vacuo*. The procedure was repeated with DCM (15 ml). The crude product (30 mg, 0.084 mmol) was dissolved in a mixture of MeCN (2 ml) and TFA

buffer (4 ml, 0.1% in bisdistilled H₂O) and purified by preparative HPLC. **1e** was obtained as a yellow oil (13 mg, 0.036 mmol, 43%).

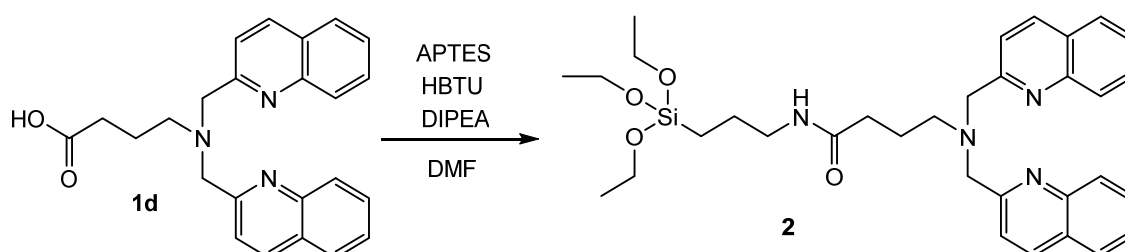
HR-MS (ESI): calcd. for [C₂₃H₂₃N₃O+H]⁺: 358.19139, found: 358.19088.

¹H NMR (400 MHz, CDCl₃) δ = 8.13 (d, J = 8.5 Hz, 2H), 8.08 (d, J = 8.5 Hz, 2H), 7.77 (d, J = 8.1 Hz, 2H), 7.70 (t, J = 7.4 Hz, 2H), 7.57 (d, J = 8.5 Hz, 2H), 7.50 (t, J = 7.5 Hz, 2H), 4.04 (s, 4H), 3.84 (t, J = 5.2 Hz, 2H), 2.89 (t, J = 5.8 Hz, 2H), 1.90-1.85 (m, 2H).

¹³C NMR (125 MHz, CDCl₃) δ = 159.69, 147.70, 136.81, 129.73, 129.01, 127.67, 127.49, 126.40, 121.08, 62.13, 60.83, 52.93, 29.02.

IR: 3309m, 3057w, 2951w, 2805m, 1734w, 1620w, 1602s, 1564m, 1504s, 1423s, 1364w, 1308m, 1223w, 1146w 1116w, 1057m, 992w, 958w, 830s, 766s.

4.1.6 Synthesis of **2**



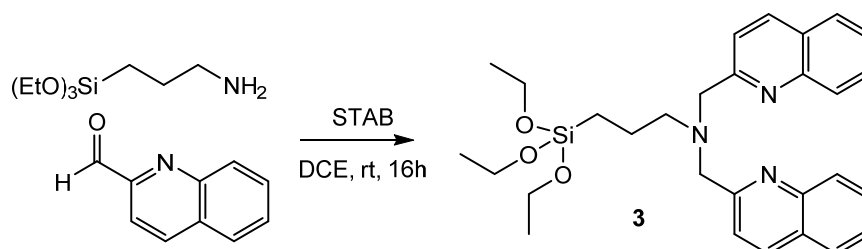
1d (28 mg, 0.07 mmol), 3-aminopropyltriethoxysilane (APTES, 17.7 mg, 18.7 μl, 0.08 mmol) and hexafluorophosphate benzotriazole tetramethyl uranium (HBTU, 82.6 mg, 0.22 mmol) were dissolved in dry DMF (3 ml) and N,N-diisopropylethylamine (DIPEA, 28 mg, 37.24 μl, 0.22 mmol) was added. The mixture was stirred at r.t. for 2h. The organic phase was washed with H₂O (3 x 10 ml), filtered and the DMF was evaporated under reduced pressure to yield **2** (35 mg, 0.06 mmol, 85%).

HR-MS (ESI): calcd. for [C₃₃H₄₅N₄O₄Si+H]⁺: 589.32119, found: 589.32046.

¹H NMR (400 MHz, CDCl₃) δ = 8.08 (d, J = 8.5 Hz, 2H), 8.04 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 8.1 Hz, 2H), 7.68 (t, J = 7.6 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 7.50 (t, J = 7.5 Hz, 2H), 4.01 (s, 4H), 3.77 (q, J = 7.0 Hz, 6H), 3.10 (q, J = 6.6 Hz, 2H), 2.68 (t, J = 6.8 Hz, 2H), 2.17 (t, J = 7.4 Hz, 2H), 1.95-1.88 (m, 2H), 1.56-1.48 (m, 2H), 1.19 (t, J = 7.0 Hz, 9H), 0.56-0.52 (m, 2H).

¹³C NMR (126 MHz, CDCl₃) δ = 172.88, 160.55, 147.69, 136.40, 129.56, 129.12, 127.65, 127.45, 126.31, 121.41, 61.52, 58.56, 54.35, 41.97, 34.66, 23.81, 23.06, 18.42, 7.90.

4.1.7 Synthesis of **3**



2-quinolinecarboxaldehyde (128 mg, 0.81 mmol) was dissolved in 1,2-dichloroethane (DCE, 20 ml) and 3-aminopropyltriethoxysilane (87 mg, 92 μl, 0.40 mmol) was added. The mixture was stirred at 25 °C for 2 h, sodium triacetoxyborohydride (STAB, 252 mg, 1.18 mmol) was added and the mixture was stirred for 3.5 h at 25 °C. 1,2-Dichloroethane was evaporated *in vacuo*, EtOH (15 ml) was added and stirred for 10 min at 25 °C. The EtOH was evaporated *in vacuo*. The residue was washed with toluene (20 ml) and the yellow solution was separated from the white precipitate by centrifugation. The

toluene was evaporated to yield crude **3**. The product was purified by flash chromatography over C-18 silica, leading to the isolation of **3** (99 mg, 0.197 mmol, 49%).

HR-MS (ESI:) calcd. for $[\text{C}_{29}\text{H}_{37}\text{N}_3\text{O}_3\text{Si}+\text{H}]^+$: 504.26770, found: 504.26794.

^1H NMR (400 MHz, CDCl_3) δ = 8.11 (d, J = 8.5 Hz, 2H), 8.04 (d, J = 8.5 Hz, 2H), 7.78-7.74 (m, 4H), 7.67 (t, J = 7.6 Hz, 2H), 7.49 (t, J = 7.4 Hz, 2H), 4.02 (s, 4H), 3.72 (q, J = 7.0 Hz, 4H), 2.63 (t, J = 7.3 Hz, 2H), 1.72-1.64 (m, 2H), 1.14 (t, J = 7.0 Hz, 9H), 0.58-0.54 (m, 2H).

^{13}C NMR (126 MHz, CDCl_3) δ = 161.0, 147.7, 136.4, 129.5, 129.2, 127.6, 127.5, 126.2, 121.2, 61.7, 58.5, 58.0, 20.8, 18.4, 8.1.

^{29}Si NMR (99.36 MHz, CDCl_3): δ = -45.01 ppm.

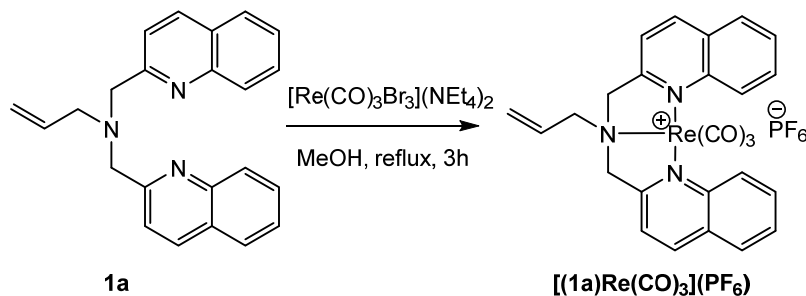
IR: 2975w, 2928w, 2881w, 1600m, 1506m, 1429w, 1390w, 1313w, 1164w, 1100s, 1074s, 950m, 831m, 767s.

4.2 Complexes

General procedure for the synthesis of $\{\text{Re}(\text{CO})_3\}^+$ -complexes

Between 0.15 and 0.01 mmol of the ligands (**1a**, **1b**, **1e**, and **3**) were dissolved in 1 to 5 ml MeOH (**3**-Re = EtOH) and equimolar amounts of $(\text{NEt}_4)_2[\text{ReBr}_3(\text{CO})_3]$ were added. A microwave vial, containing the reaction solution was purged with N_2 for 5 min. The mixture was heated to 85°C (110°C for $[(\text{1e})\text{Re}(\text{CO})_3]^+$ and **3**-Re) for 45 min in a microwave reactor. H_2O was added to the vial and the formed precipitate was removed by filtration or centrifugation. From the clear solution the product was precipitated by the addition of NH_4PF_6 as the corresponding PF_6 -salt and collected by filtration or centrifugation. $[\text{3-Re}](\text{PF}_6)$ was directly precipitated from the aqueous solution by the addition of NH_4PF_6 . The products were washed with few ml of H_2O and dried under high vacuum.

4.2.1 Analytical data for $[(\text{1a})\text{Re}(\text{CO})_3](\text{PF}_6)$



HR-MS (ESI:) calcd. for $[\text{C}_{26}\text{H}_{21}\text{N}_3\text{O}_3\text{Re}]^+$: 610.11349, found: 610.11355.

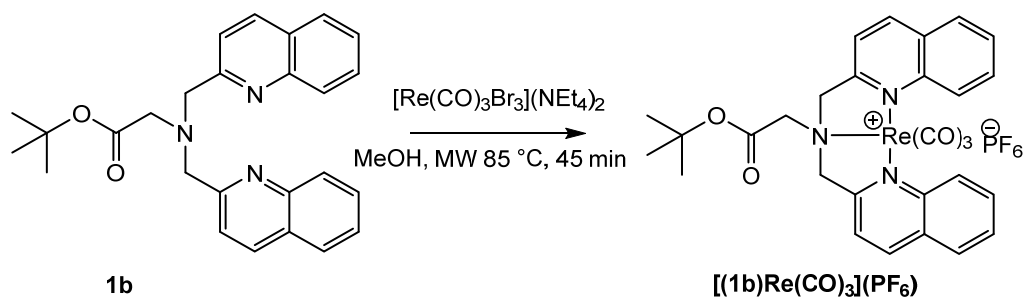
^1H NMR (500 MHz, CDCl_3) δ = 8.48 (d, J = 8.8 Hz, 2H), 8.36 (d, J = 8.4 Hz, 2H), 7.90 (d, J = 8.0 Hz, 2H), 7.84 (t, J = 7.5 Hz, 2H), 7.66 (m, 4H), 6.31 (m, 1H), 5.77 (d, J = 16.8 Hz, 1H), 5.69 (d, J = 10.2 Hz, 1H), 5.08 (m, 4H), 4.32 (d, J = 7.1 Hz, 2H).

^{13}C NMR (125 MHz, CDCl_3) δ = 195.62, 194.14, 164.48, 147.11, 141.89, 133.24, 129.82, 129.59, 128.58, 128.54, 128.43, 127.34, 120.17, 70.42, 68.85.

IR: 2026s (CO), 1903s (CO), 1712w, 1604w, 1516w, 1432w, 1369w, 1291w, 1217w, 1149w, 1124w, 948w, 835s 747w.

Crystals suitable for X-ray diffraction analysis were obtained by vapor diffusion of cyclohexane into a THF solution of $[(\text{1a})\text{Re}(\text{CO})_3](\text{PF}_6)$.

4.2.2 Analytical data for [(1b)Re(CO)₃](PF₆)



HR-MS (ESI:) calcd. for [C₂₉H₂₇N₃O₅Re]⁺: 684.15027, found: 684.14980.

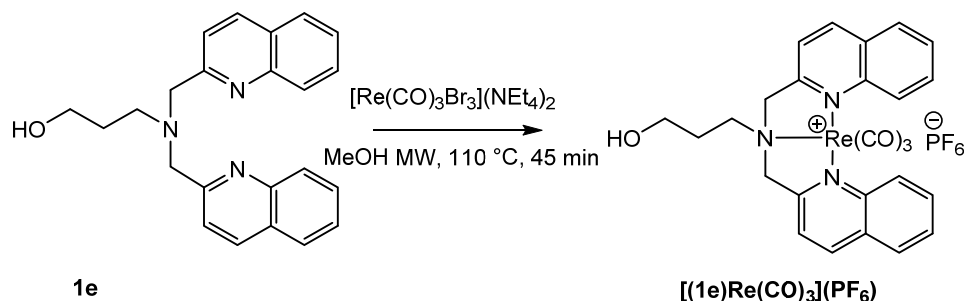
¹H NMR (400 MHz, CDCl₃) δ = 8.49 (d, *J* = 8.7 Hz, 2H), 8.34 (d, *J* = 8.4 Hz, 2H), 7.91 (dd, *J* = 3.1 Hz, 2H), 7.85-7.81 (m, 2H), 7.66 (t, *J* = 7.2 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 5.25-5.13 (m, 4H), 4.48 (s, 2H), 1.45 (s, 9H).

¹³C NMR (125 MHz, CDCl₃) δ = 195.54, 193.76, 166.65, 164.76, 147.02, 141.62, 133.15, 129.81, 128.59, 128.52, 128.30, 119.74, 84.83, 70.40, 66.83, 28.09.

IR: 2159w, 2027s (CO), 1910s (CO), 1735w, 1519w, 1370w, 1243w, 1160m, 1034w, 844s, 780w.

Crystals suitable for X-ray diffraction analysis were obtained by vapor diffusion of cyclohexane into a THF solution of [(1b)Re(CO)₃](PF₆).

4.2.3 Analytical data for [(1e)Re(CO)₃](PF₆)



HR-MS (ESI:) calcd. for [C₂₆H₂₂N₃O₄Re]⁺: 628.12406, found: 628.12394.

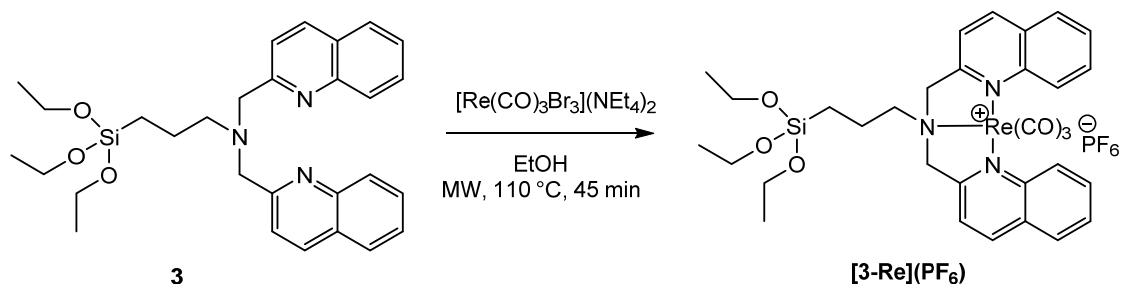
¹H NMR (400 MHz, CDCl₃) δ = 8.47 (d, *J* = 3.1 Hz, 2H), 8.35 (d, *J* = 8.3 Hz, 2H), 7.89 (d, *J* = 3.2 Hz, 2H), 7.85-7.81 (m, 2H), 7.68-7.63 (m, 4H), 5.16-5.04 (m, 4H), 3.99-3.95 (m, 2H), 3.84 (t, *J* = 5.6 Hz, 2H), 2.30-2.23 (m, 2H).

¹³C NMR (126 MHz, CDCl₃) δ = 195.72, 194.15, 164.64, 147.10, 141.87, 133.21, 129.78, 128.59, 128.55, 128.43, 120.21, 68.70, 65.93, 59.80, 29.23.

IR: 3617w, 2919w, 2025s (CO), 1932m (CO), 1897s (CO) 1597w, 1519w, 1435w, 1371w, 1306w, 1214w, 1126w, 1047w, 831s, 742m, 659m.

Crystals suitable for X-ray diffraction analysis were obtained by vapor diffusion of cyclohexane into a THF solution of [(1e)Re(CO)₃](PF₆).

4.2.4 Analytical data for [3-Re](PF₆)



HR-MS (ESI:) calcd. for [C₃₂H₃₇N₃O₆ReSi]⁺: 774.20036, found: 774.20035.

¹H NMR (500 MHz, CDCl₃) δ = 8.46 (d, *J* = 8.8 Hz, 2H), 8.33 (d, *J* = 8.5 Hz, 2H), 7.88 (d, *J* = 8.0 Hz, 2H), 7.83-7.80 (m, 2H), 7.66-7.63 (m, 4H), 5.19-4.96 (m, 4H), 3.84 (q, *J* = 7.0 Hz, 6H), 2.16-2.10 (m, 2H), 1.58 (s, 2H), 1.20 (t, *J* = 7.0 Hz, 9H), 0.75 (t, *J* = 7.7 Hz, 2H).

¹³C NMR (126 MHz, CDCl₃) δ = 195.8, 194.2, 164.7, 147.1, 141.8, 133.1, 129.8, 128.6, 128.5, 128.4, 120.3, 70.7, 68.7, 58.8, 20.4, 18.4, 7.7.

²⁹Si NMR (99.38 MHz, CDCl₃): δ = -47.44 ppm.

IR: 2976w, 2891w, 2025s (CO), 1901s (CO), 1603w, 1517w, 1470w, 1436w, 1394w, 1300w, 1205w, 1163w, 1073m, 958w, 873w, 835s, 779m, 749m, 647w.

UV-Vis (CHCl₃, 10⁻⁵ M): 323 nm (13696 M⁻¹cm⁻¹).

Fluorescence (CHCl₃, 10⁻⁵ M): λ_{ex} (326), λ_{em} air (426, 546), λ_{em} N₂ (383, 566).

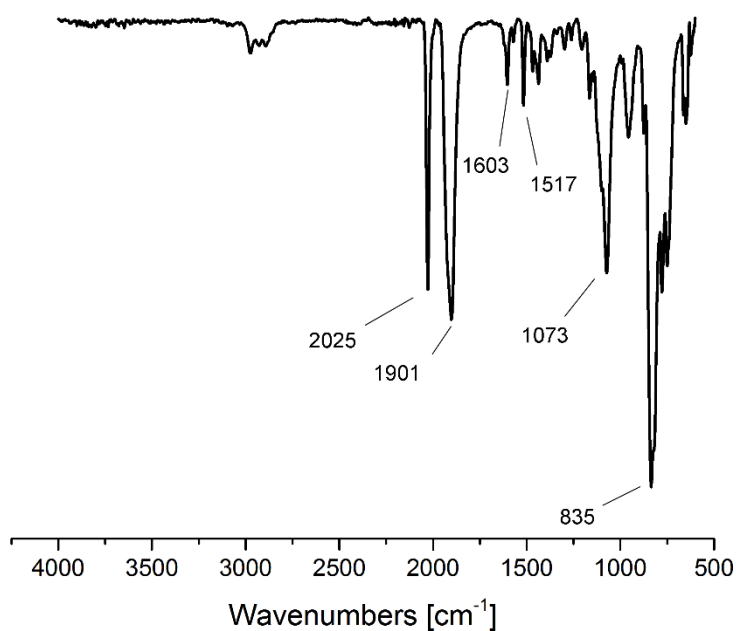
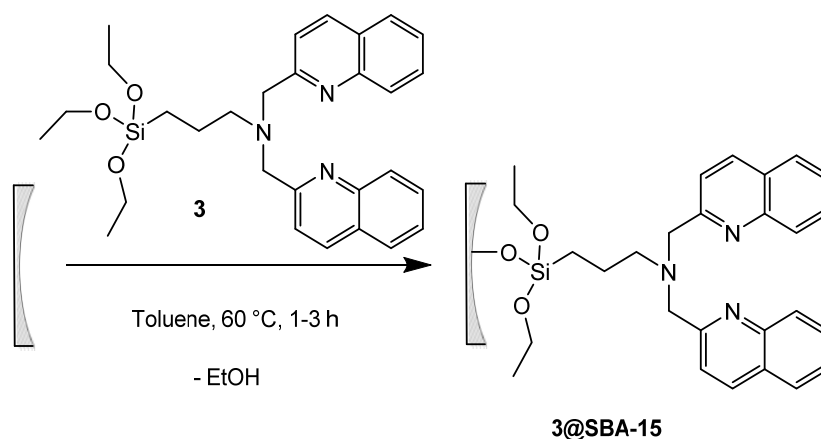


Figure S4.2.4.1: IR spectrum of [3-Re](PF₆).

4.3 Functionalized Mesoporous Silica Particles

4.3.1 Synthesis of **3@SBA-15**



SBA-15 particles (213 mg) were dried by heating (140 °C) under high vacuum for 4 h. **3** (10 mg, 0.02 mmol) was dissolved in dry toluene (5 ml) and added to the SBA-15 particles. The suspension was sonicated at 60 °C for 2 h. Filtration, washing with toluene (5 ml) and Et₂O (5 ml) and drying under high vacuum led to the isolation of **3@SBA-15** (176 mg).

EA: C 2.46, H 0.49, N 0.32 (0.08 mmol **3**/g particle, based at the N content)

SBA-15 particles with higher **3** content were synthesized by the following procedure:

SBA-15 particles (100 mg) were dried by heating (140 °C) under high vacuum for 4 h. **3** (200 mg, 0.4 mmol) was dissolved in dry toluene (2.5 ml) and added to the SBA-15 particles. The suspension was sonicated at 60 °C for 2 h. Filtration, washing with toluene (5 ml) and Et₂O (5 ml) and drying under high vacuum led to the isolation of **3@SBA-15** (111 mg).

EA: C 10.00, H 1.10, N 1.55 (0.37 mmol **3**/g particle, based at the N content)

HR-ESI of dissolved particles (1M NaOD in D₂O): calc. for [C₂₃H₂₅O₃N₃Si+H]⁺: 420.17379, found: 420.17345.

¹H-NMR (1M NaOD in D₂O 500 MHz): δ = 7.76 (d, *J* = 8.5 Hz, 2H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.52-7.49 (m, 4H), 7.34 (t, *J* = 7.0 Hz, 2H), 7.24 (d, *J* = 8.5 Hz, 2H), 3.88 (s, 4H), 2.70 (t, *J* = 7.8 Hz, 2H), 1.72-1.69 (m, 2H), 0.38 (t, *J* = 8.4 Hz, 2H).

4.3.2 Synthesis of **3@SBA-15** via co-condensation

0.22 g of Pluronic P123 (structure directing agent) was dissolved in 8 mL of 1.55 M hydrochloric acid. Once a clear solution was obtained, 0.5 mL of TEOS was slowly added. Afterwards **3** (22mg, 0.044 mmol, **3**:TEOS 1:50) was added to the solution. The mixture was stirred for 20 h at 35 °C, transferred to a Teflon-lined autoclave, and placed in a preheated oven at 100 °C for 24 h. The autoclave was allowed to cool to room temperature before the product was recovered by filtration and washed with at least 1 L of H₂O. The material was allowed to dry at room temperature overnight. The template was removed by extraction with acidified ethanol.

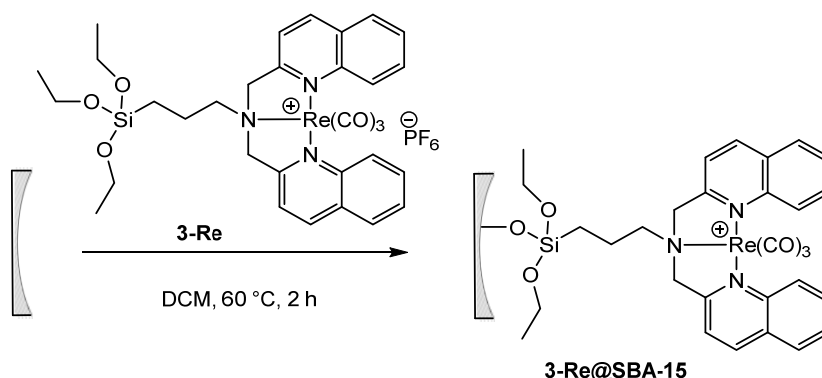
EA: 12.13% C, 2.58% H, 0.49% N (0.12 mmol **3**/g particle, based at the N content).

Nitrogen sorption: BET: 345 m²/g; average pore size: 7.3 nm; total pore volume: 0.6 cm³/g.

IR: 1634w, 1459w, 1377w, 1057s (Si-O), 946m, 801m.

4.3.3 Synthesis of **3-Re@SBA-15**

Method a)

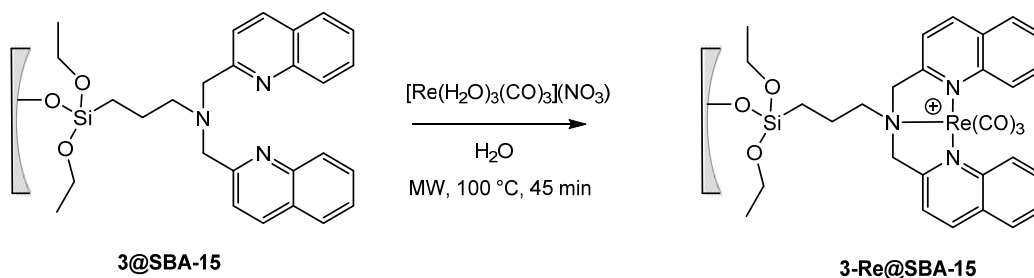


SBA-15 particles were dried by heating (140 °C) under high vacuum for 4 h. The dry SBA-15 particles (200 mg) were dispersed in dry DCM (5 ml). The suspension was transferred into a microwave vial and [**3-Re**](PF₆) (9.2 mg, 0.01 mmol) was added. The suspension was sonicated for 2 h at 60 °C. After filtration, washing with DCM (3 ml) and drying under high vacuum **3-Re@SBA-15** (202 mg) was isolated.

EA: Found: C 2.70, H 0.57, N 0.21 (0.05 mmol **3-Re**/g particle, based at the N content).

IR: 2026w (CO), 1901w (CO), 1891w (CO), 1631w, 1053s (Si-O), 964m, 818w, 649w.

Method b)



(NEt₄)₂[Re(CO)₃Br₃] (38.4 mg, 0.05 mmol) was dissolved in H₂O (6 ml) and AgNO₃ (25 mg, 0.15 mmol) was added. The solution turned milky and a precipitate was formed immediately. After stirring for 60 min at r.t. the precipitate was filtered off. A clear solution [Re(H₂O)₃(CO)₃](NO₃) was obtained (pH 6-7). This solution was added to 80 mg of **3@SBA-15** particles, which contained 0.08 mmol **3**/g particles (based on the N content determined by EA). The suspension was heated at 100 °C for 45 min in a microwave reactor. Finally, **3-Re@SBA-15** (71 mg) was isolated by filtration, washed with H₂O (2 ml) and toluene (4 ml) and dried under vacuum.

EA: C: 2.28 H: 0.80 N: 0.30 (0.07 mmol **3**/g particle, based at the N content)

Nitrogen sorption: BET: 217 m²/g; average pore size: 7.0 nm; total pore volume: 0.43 cm³/g

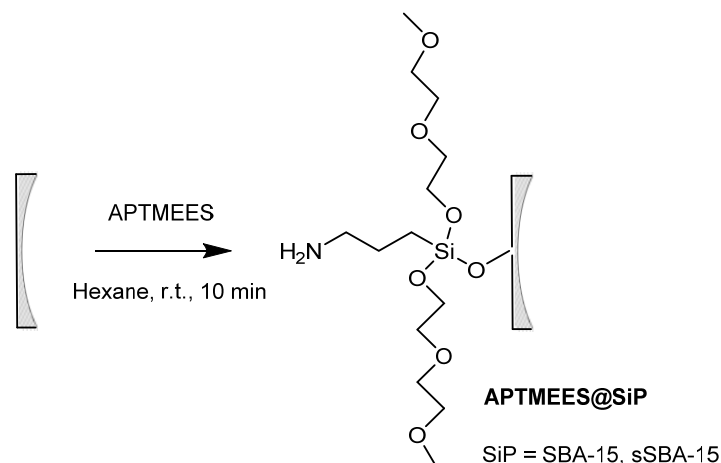
IR: 2026w (CO), 1901w (CO), 1891w (CO), 1631w, 1053s (Si-O), 964m, 818w, 649w.

ICP-MS: 1.4 %w; 0.077 mmol/g particles; 0.07 Re atoms/nm²

Control reaction

Unmodified **SBA-15** particles have been treated under the same reaction condition as for the synthesis of **3-Re@SBA-15**. In contrast to **3-Re@SBA-15**, no CO vibrations in the IR spectrum of these **SBA-15** particles can be observed. ICP-MS measurements showed a Re loading of: 0.3%w, 0.014 mmol/g particles; 0.014 Re atoms/nm².

4.3.4 Synthesis of APTMEES@SiP



SBA-15

SBA-15 particles (300 mg) were dried by heating (140 °C) under high vacuum for 4 h. The dry particles were dispersed in hexane (15 ml) and 3-aminopropyltris(methoxyethoxyethoxy)silane (APTMEES, 26.7 mg, 0.06 mmol, 25 μ l) was added. The suspension was sonicated for 10 min at r.t. The particles were recovered (308 mg) by filtration, washed with hexane (3 \times 3 ml) and dried under high vacuum.

EA: Found: C 3.89, H 1.15, N 0.35.

Nitrogen sorption: BET: 540 m²/g; average pore size: 7.3 nm; total pore volume: 0.80 cm³/g. (corresponding batch of unmodified SBA-15: BET: 663 m²/g; average pore size: 7.3 nm; total pore volume: 0.89 cm³/g)

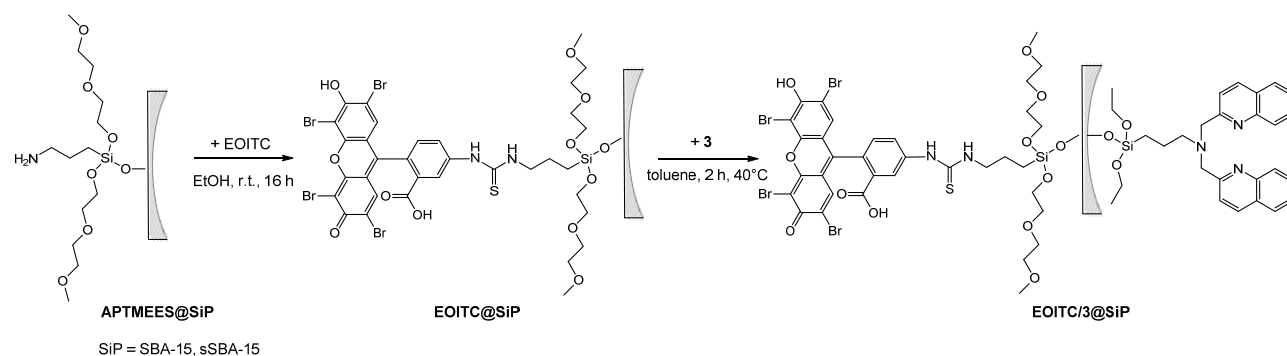
sSBA-15

sSBA-15 particles (900 mg) were dried by heating (140 °C) under high vacuum for 4 h. The dry particles were dispersed in hexane (35 ml) and 3-aminopropyltris(methoxyethoxyethoxy)silane (APTMEES, 78 mg, 0.18 mmol, 75 μ l) was added. The suspension was sonicated for 10 min at r.t. The particles were recovered (904 mg) by filtration, washed with hexane (3 \times 3 ml) and dried under high vacuum.

EA: Found: C 3.63, H 1.07, N 0.35.

Nitrogen sorption: BET: 532 m²/g; average pore size: 4.9 nm; total pore volume: 0.51 cm³/g.

4.3.5 Synthesis of EOITC/3@SiP



sSBA-15

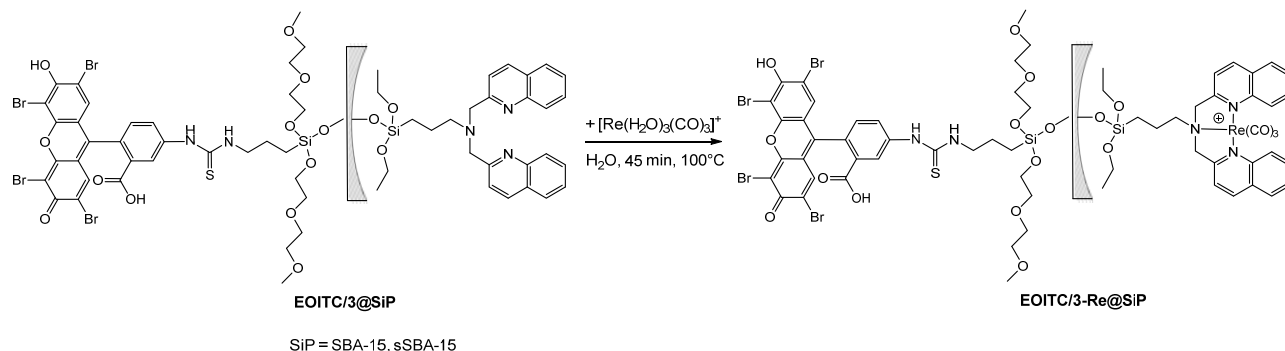
Eosin isothiocyanate (EOITC, 4.2 mg, 6.0 μ mol) was dissolved in EtOH (10 ml). APTMEES@sSBA-15 particles (310 mg) were added and the suspension was stirred at r.t. for 16 h. The particles were

collected by filtration, washed with EtOH (50 ml) and H₂O (50 ml), yielding **EOITC/@sSBA-15** (297 mg). **3** (10 mg, 0.02 mmol) was dissolved in dry toluene (5 ml) and added to dry **EOITC/@sSBA-15** particles (200 mg). The suspension was sonicated at 40 °C for 2 h. Finally, **EOITC/3@sSBA-15** (186 mg) was filtered off, washed with toluene (5 ml) and Et₂O (5 ml) and dried under high vacuum.

SBA-15

EOITC/3@sBA-15 was synthesized following the same procedure as for the synthesis of **EOITC/3@sSBA-15**.

4.3.6 Synthesis of **EOITC/3-Re@SiP**



sSBA-15

(NEt₄)₂[Re(CO)₃Br₃] (51.2 mg, 0.066 mmol) was dissolved in H₂O (8 ml) and 3 eq. AgNO₃ (33.6 mg, 0.198 mmol) were added. A colorless precipitate was formed immediately. After stirring for 60 min at r.t. the precipitate was filtered off. A clear solution of [Re(H₂O)₃(CO)₃]NO₃ was obtained (pH 6-7). This solution was added to the **EOITC/3@sSBA-15** (100 mg) and the suspension was heated at 100 °C for 45 min by means of a microwave reactor. The formed **EOITC/3-Re@sSBA-15** (72 mg) particles were collected by filtration, washed with H₂O (2 ml) and toluene (4 ml) and dried under vacuum. **EOITC/3@sSBA-15** was characterized by CLSM.

SBA-15

EOITC/3-Re@sBA-15 was synthesized following the same procedure as for the synthesis of **EOITC/3-Re@sSBA-15**.

4.4 Labeling of Silica Particles (SiP) with [^{99m}Tc(H₂O)₃(CO)₃]⁺

4.4.1 Synthesis of [^{99m}Tc(H₂O)₃(CO)₃]⁺

[^{99m}Tc(CO)₃(H₂O)₃]⁺ was synthesized according to an adapted version of a published procedure.[7] The [^{99m}TcO₄]⁻ eluate (1 - 2 ml, obtained from the ⁹⁹Mo/^{99m}Tc generator) was added to a N₂-flushed microwave tube containing Na₂(BH₃CO₂) (4 mg, 0.040 mmol), disodium tartrate dihydrate (7.0 mg, 0.030 mmol), and disodium tetraborate pentahydrate (7 mg, 0.024 mmol) and heated in a microwave reactor for 10 min at 110°C. Finally, the pH of the solution was adjusted to pH 7 by the addition of 80 – 100 µl 1 M HCl.

4.4.2 Synthesis of **3-^{99m}Tc@sBA-15**

A microwave vial was charged with **3@sBA-15** (10 mg) and saline (2 ml). The vial was flushed with N₂ (5 min). [^{99m}Tc(H₂O)₃(CO)₃]⁺ (5 - 15 MBq) in saline (2 ml, pH 7) was added and the suspension was heated at 100 °C for 15 min in the microwave reactor. For reaction control an aliquot (0.5 ml) was

filtered and centrifuged and the clear solution was used for radio-HPLC measurements. As an additional control 10 μl of the centrifuged sample were collected and the remaining activity in solution was determined by means of a γ -counter. Labeling yield >99%.

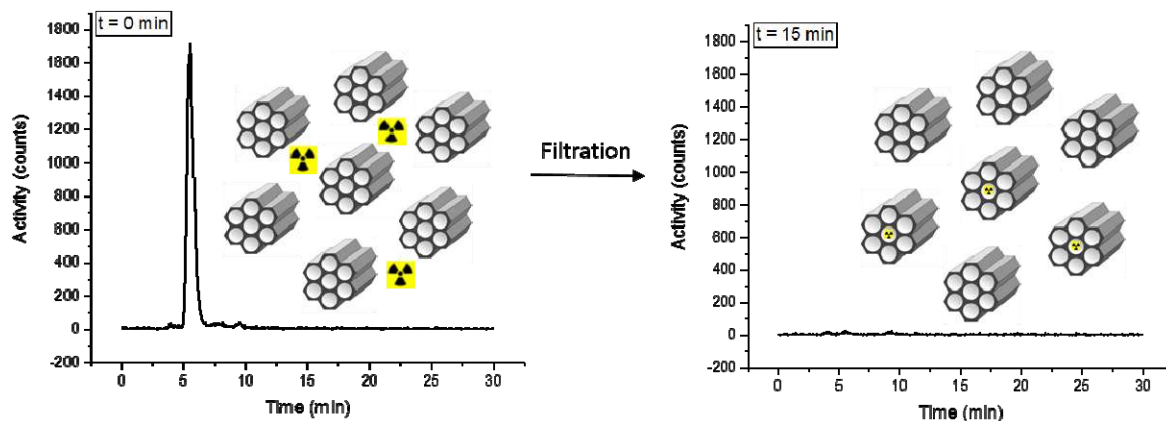


Figure S4.4.2.1: Idealized picture of the labeling of **3@SBA-15** with $[\text{}^{99\text{m}}\text{Tc}(\text{H}_2\text{O})_3(\text{CO})_3]^+$. Since **3** is randomly distributed over the surface of these model particles, the labeling with $^{99\text{m}}\text{Tc}$ is not preferentially in the pores. The radio-HPLC traces show the activity in the reaction solution. Left: The γ -signal of $[\text{}^{99\text{m}}\text{Tc}(\text{H}_2\text{O})_3(\text{CO})_3]^+$ is observed at 5.5 min (reaction time = 0). Right: almost quantitative coordination of $[\text{}^{99\text{m}}\text{Tc}(\text{H}_2\text{O})_3(\text{CO})_3]^+$ at the **3@SBA-15** particles (reaction time = 15 min) evidenced by disappearance of the 5.5 min peak.

Control reaction of **SBA-15** with $[\text{}^{99\text{m}}\text{Tc}(\text{H}_2\text{O})_3(\text{CO})_3]^+$

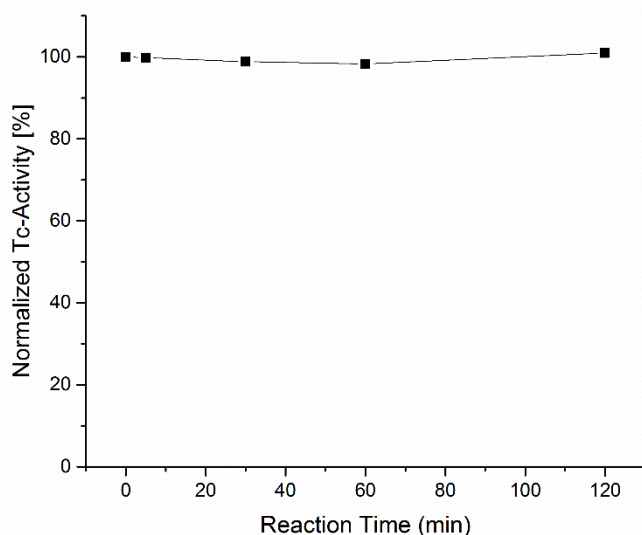
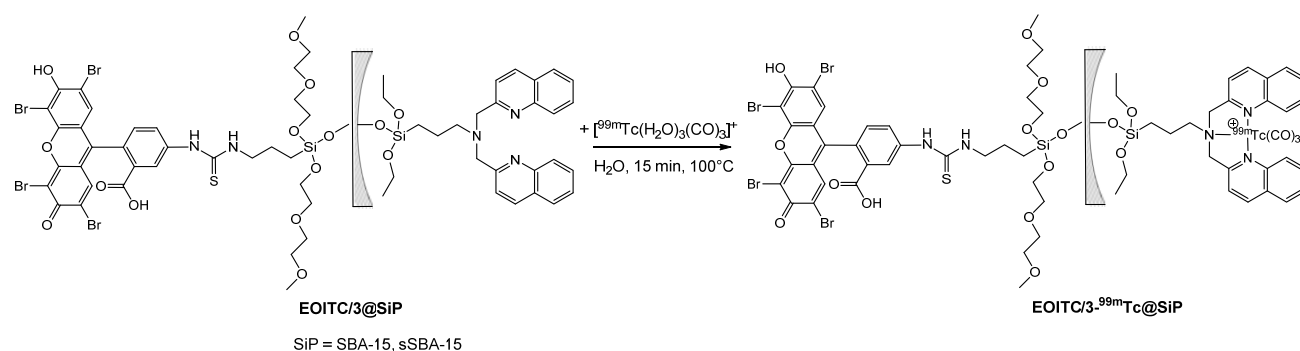


Figure S4.4.2.2: Control reaction of **SBA-15** particles with $[\text{}^{99\text{m}}\text{Tc}(\text{H}_2\text{O})_3(\text{CO})_3]^+$. Under the same reaction condition as applied for the labelling of **3@SBA-15** with $[\text{}^{99\text{m}}\text{Tc}(\text{H}_2\text{O})_3(\text{CO})_3]^+$, no decrease of activity in the reaction solution can be observed.

4.4.3 Synthesis of **3-Re^{99m}Tc@SBA-15**

A microwave vial was charged with **3-Re@SBA-15** (10 mg) and saline (2 ml). The vial was flushed with N₂ (5 min). [^{99m}Tc(H₂O)₃(CO)₃]⁺ (5 - 15 MBq) in saline (2 ml, pH 7) was added and the suspension was heated at 100 °C for 15 min in the microwave reactor. For reaction control an aliquot (0.5 ml) was filtered and centrifuged and the clear solution was used for radio-HPLC measurements. As an additional control 10 µl of the centrifuged sample were collected and the remaining activity in solution was determined by means of a γ-counter. Labeling yield 52%.

4.4.4 Synthesis of **EOITC/3-^{99m}Tc@SiP**



A microwave vial was charged with **EOITC/3@SiP** (SiP = SBA-15, sSBA-15) (10 mg) and saline (2 ml). The vial was flushed with N₂ (5 min). [^{99m}Tc(H₂O)₃(CO)₃]⁺ (5 - 15 MBq) in saline (2 ml, pH 7) was added and the suspension was heated at 100 °C for 15 min in the microwave reactor. For reaction control an aliquot (0.5 ml) was filtered and centrifuged and the clear solution was used for radio-HPLC measurements. As an additional control 10 µl of each centrifuged sample were collected and the remaining activity in solution was determined by means of a γ-counter. Labeling yield 79%.

5. Spectra

5.1 ^1H - and ^{13}C -NMR of **1a**

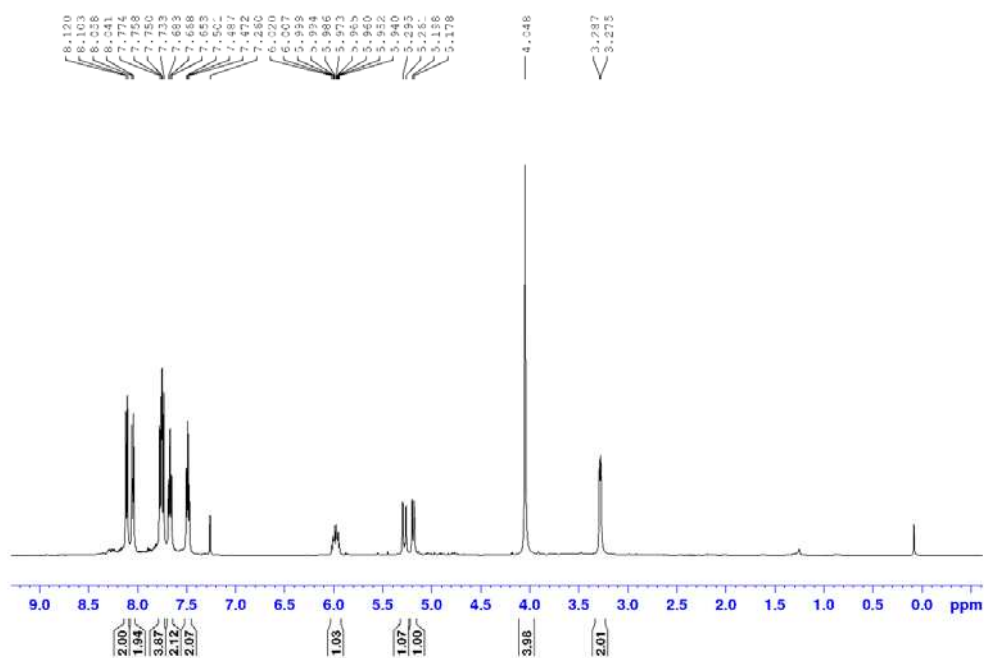


Figure S5.1.1: ^1H -NMR of **1a** in CDCl_3 .

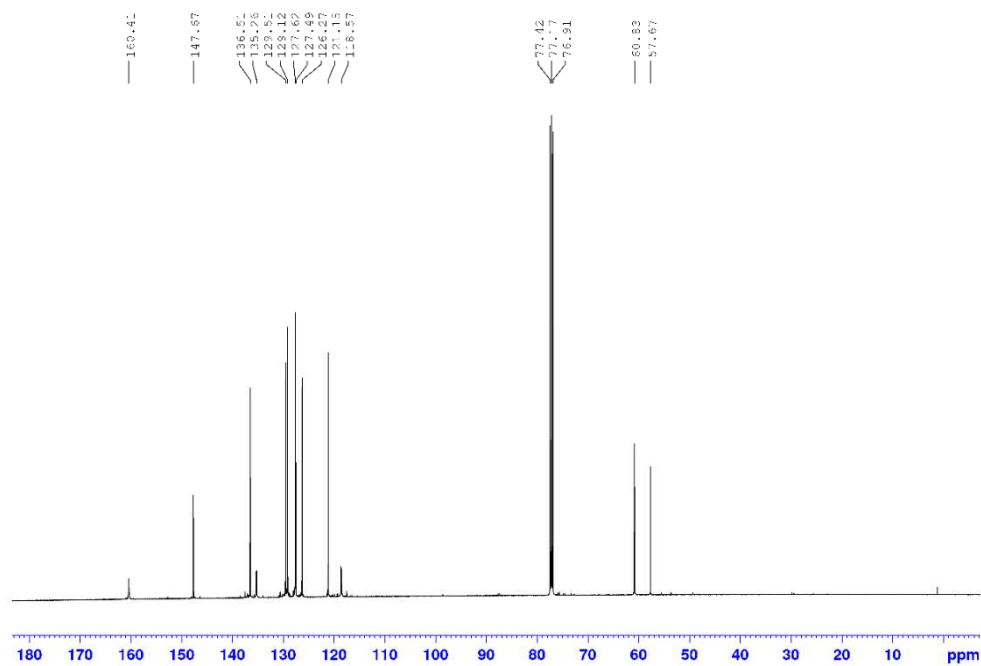


Figure S5.1.2: ^{13}C -NMR of **1a** in CDCl_3 .

5.2 ^1H - and ^{13}C -NMR of **1b**

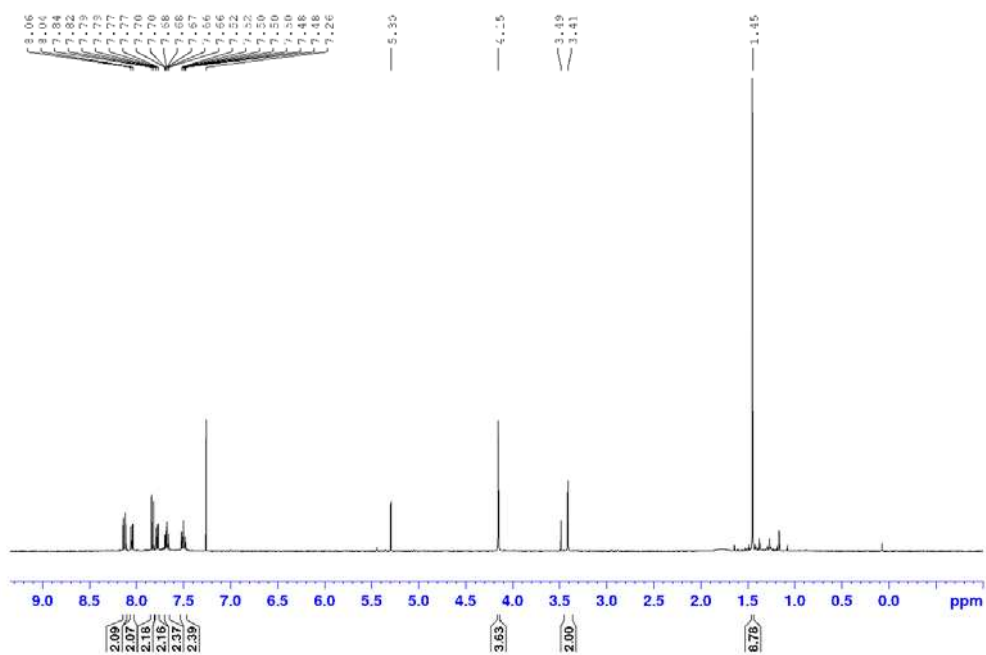


Figure S5.2.1: ^1H -NMR of **1b** in CDCl_3 .

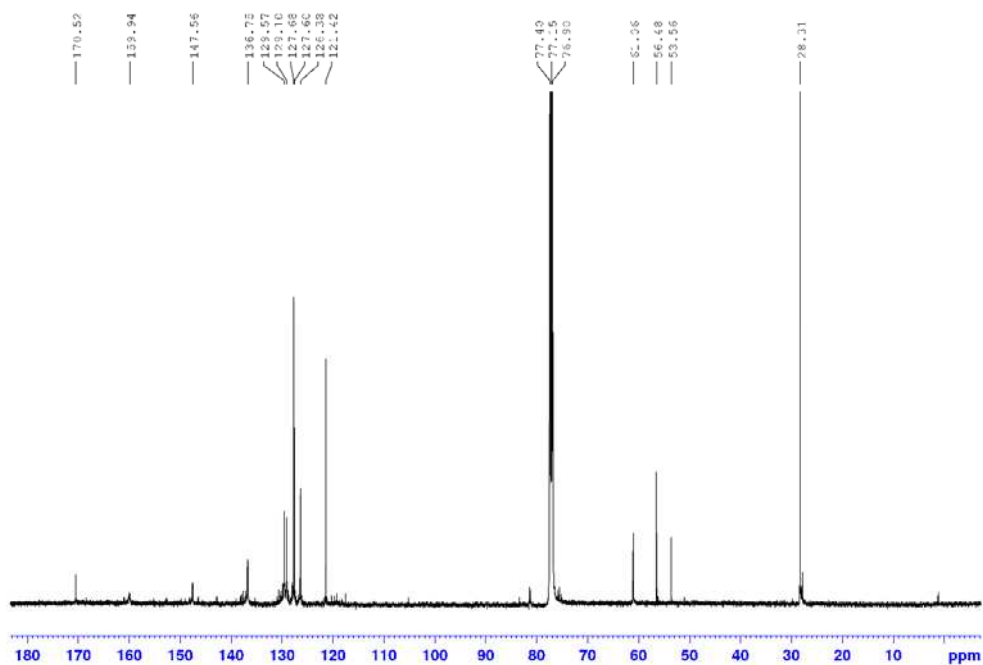


Figure S5.2.2: ^{13}C -NMR of **1b** in CDCl_3 .

5.3 ^1H - and ^{13}C -NMR of **1c**

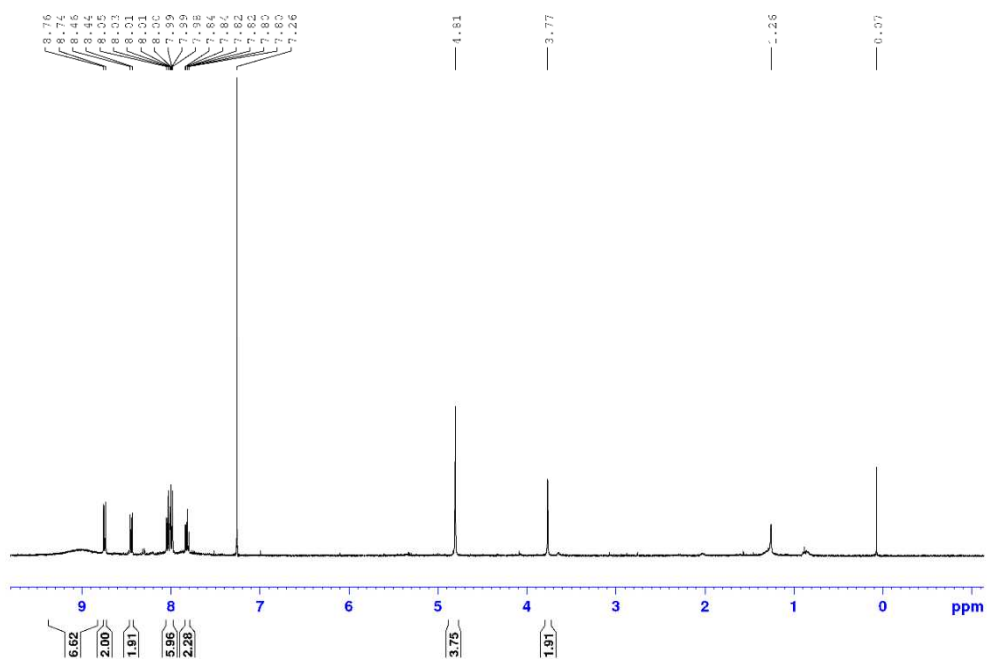


Figure S5.3.1: ^1H -NMR of **1c** in CDCl_3 .

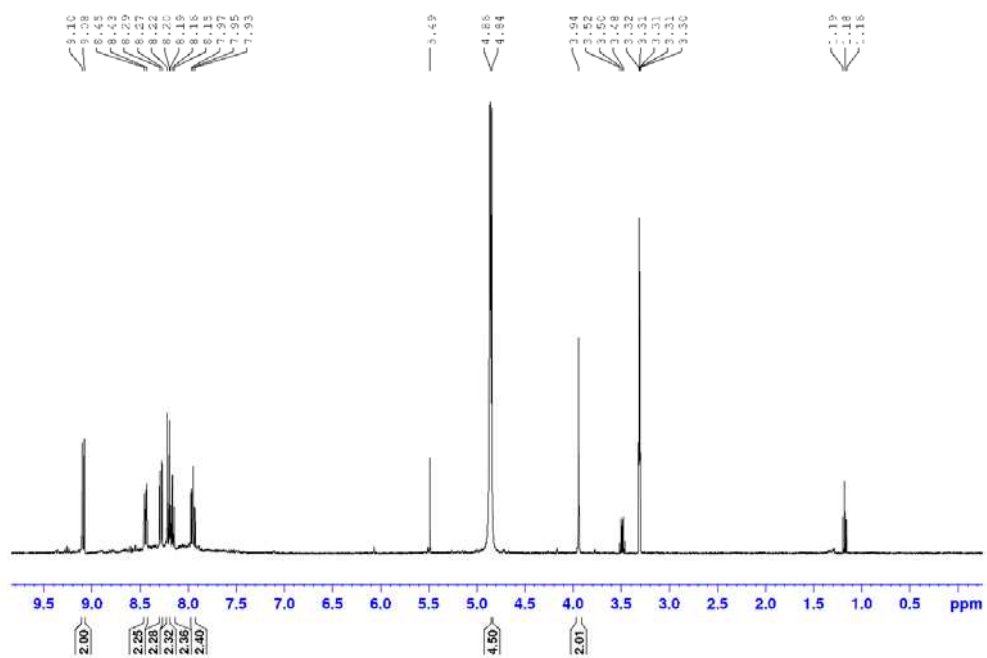


Figure S5.3.2: ^{13}C -NMR of **1c** in MeOD .

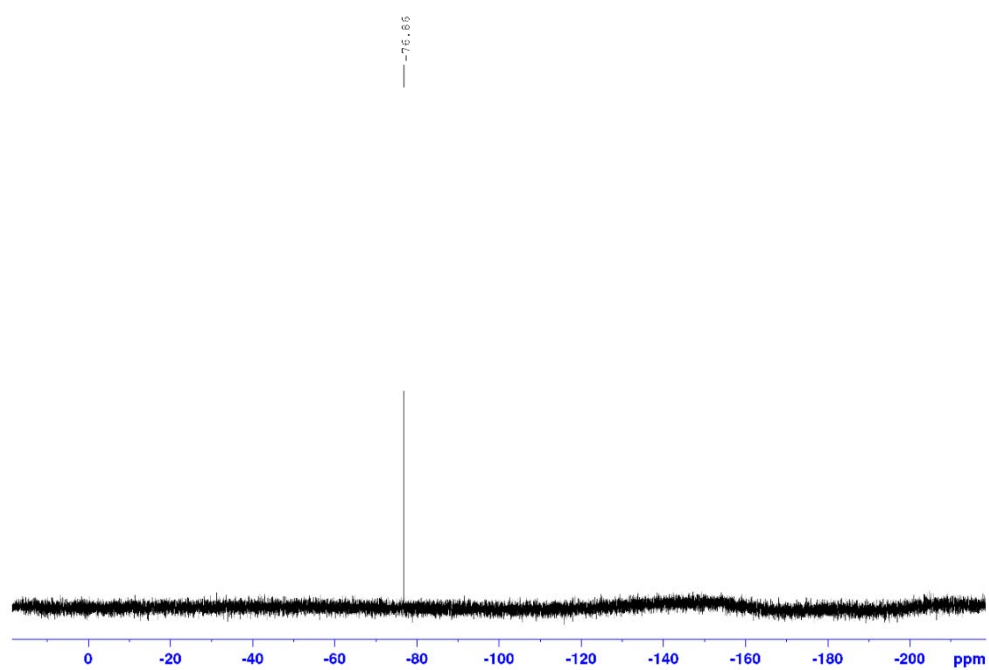


Figure S5.3.3: ^{19}F -NMR of **1c**.

5.4 ^1H - and ^{13}C -NMR of **1d**

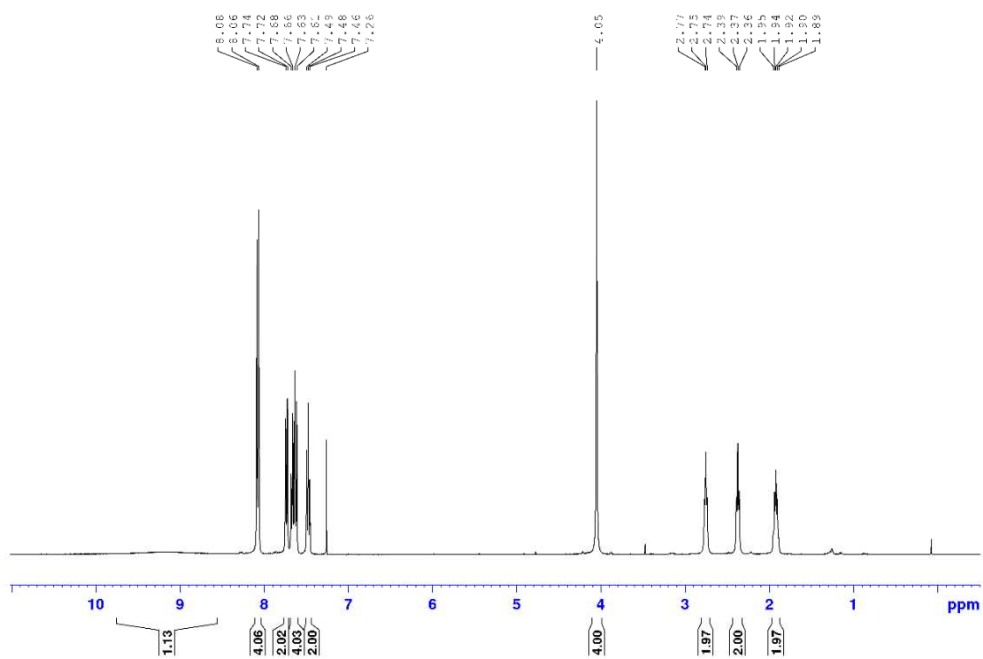


Figure S5.4.1: ^1H -NMR of **1d** in CDCl_3 .

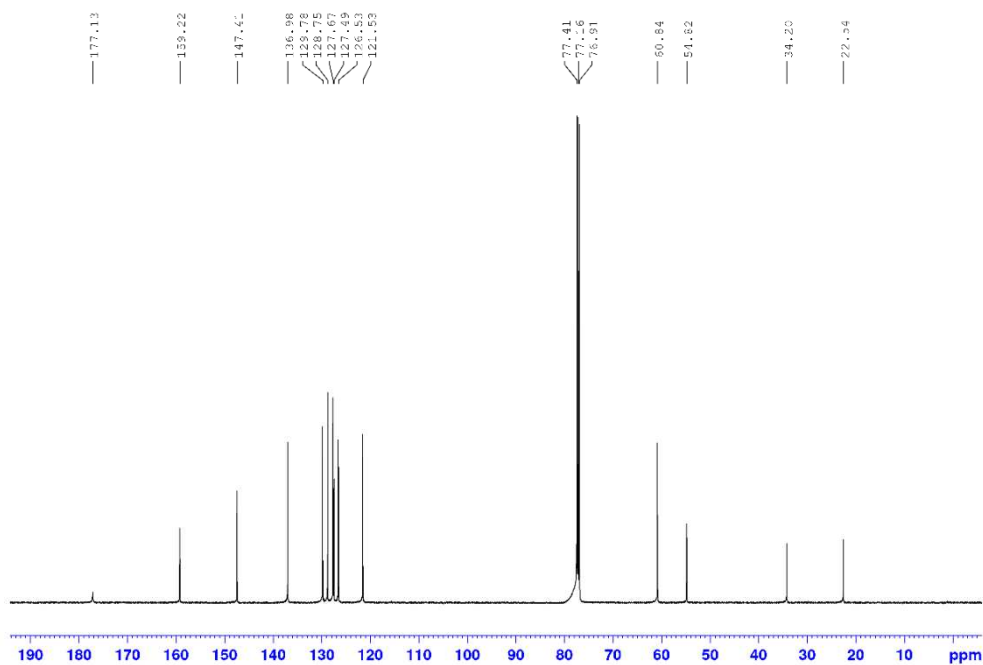


Figure S5.4.2: ^{13}C -NMR of **1d** in CDCl_3 .

5.5 ^1H - and ^{13}C -NMR of **1e**

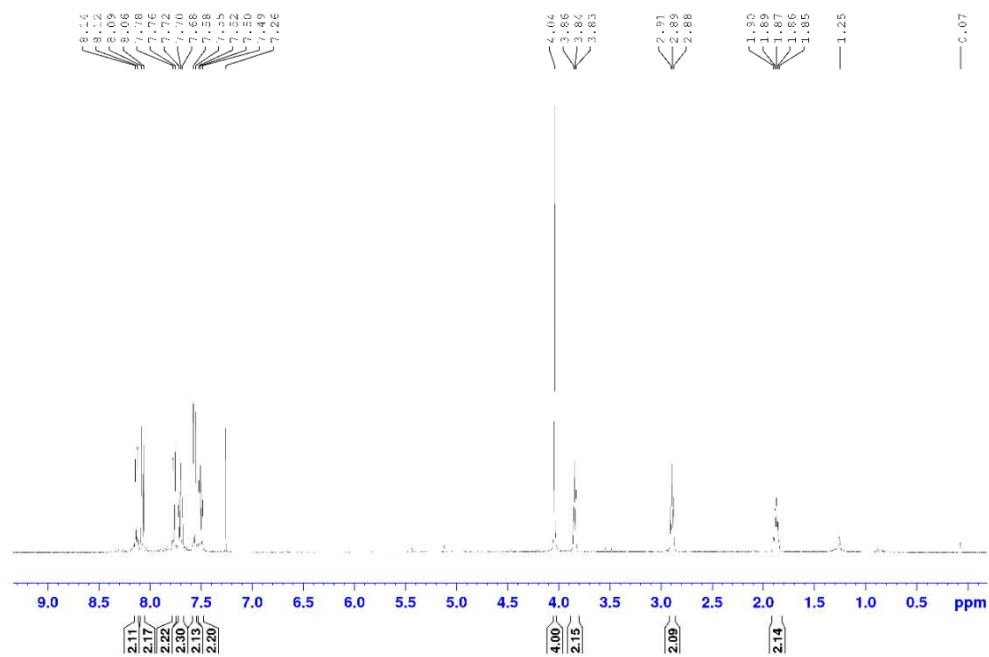


Figure S5.5.1: ^1H -NMR of **1e** in CDCl_3 .

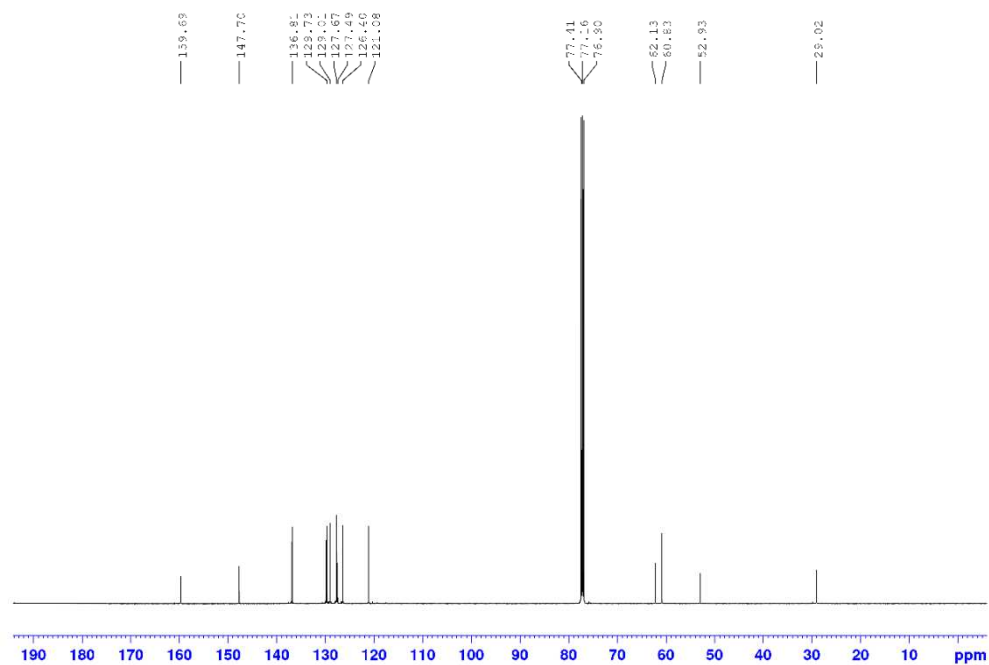


Figure S5.5.2: ^{13}C -NMR of **1e** in CDCl_3 .

5.6 ^1H - and ^{13}C -NMR of **2**

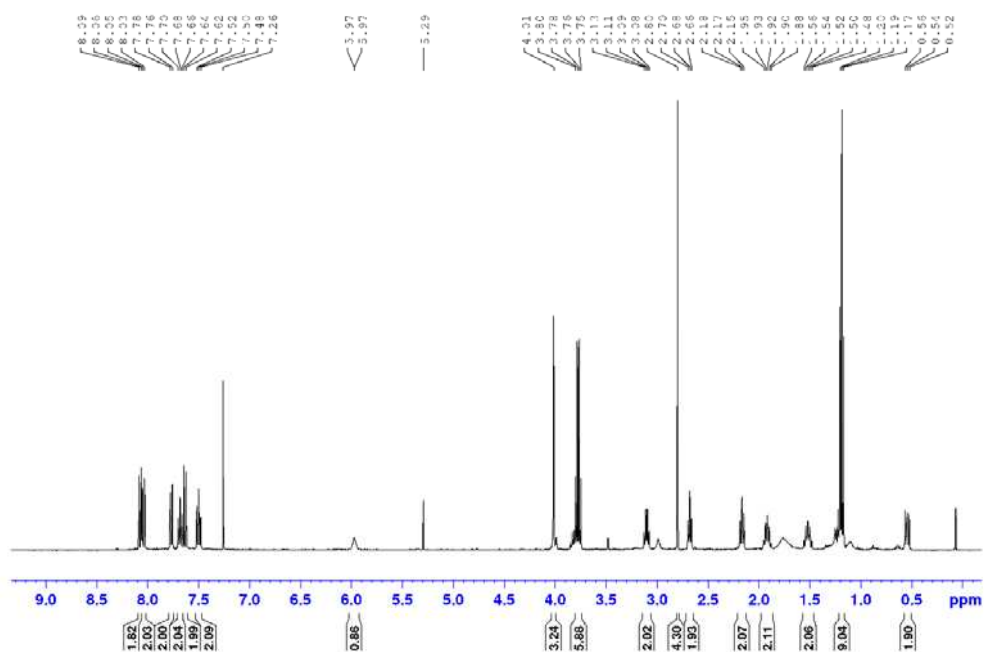


Figure S5.6.1: ^1H -NMR of **2** in CDCl_3 .

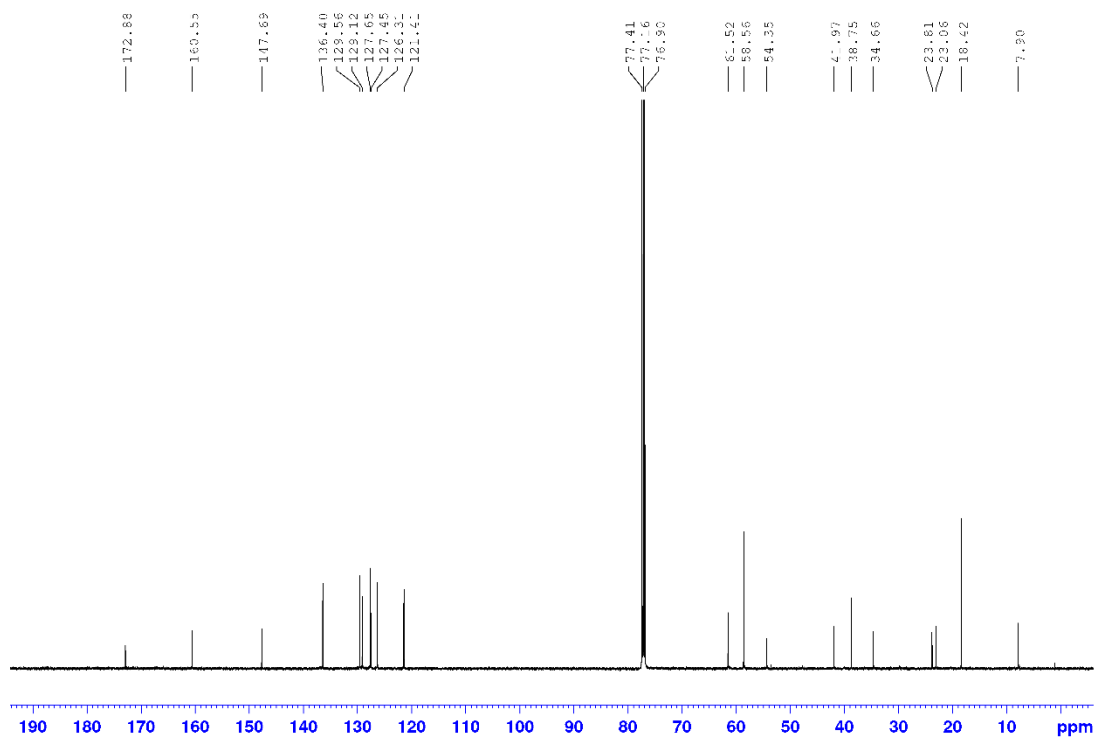


Figure S5.6.2: ^{13}C -NMR of **2** in CDCl_3 .

5.7 ^1H - and ^{13}C -NMR of **3**

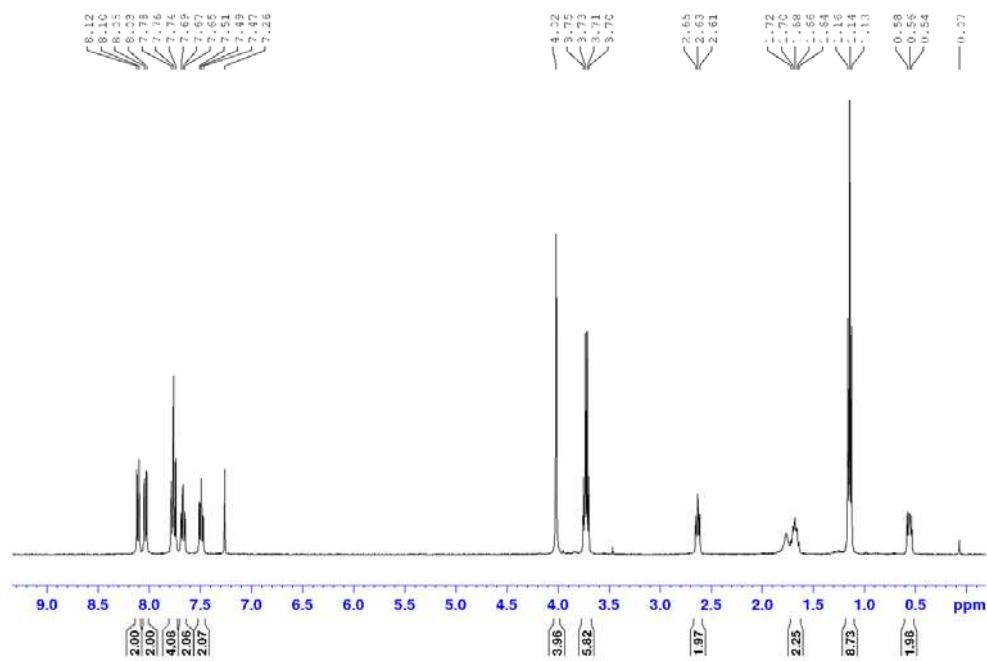


Figure S5.7.1: ^1H -NMR of **3** in CDCl_3 .

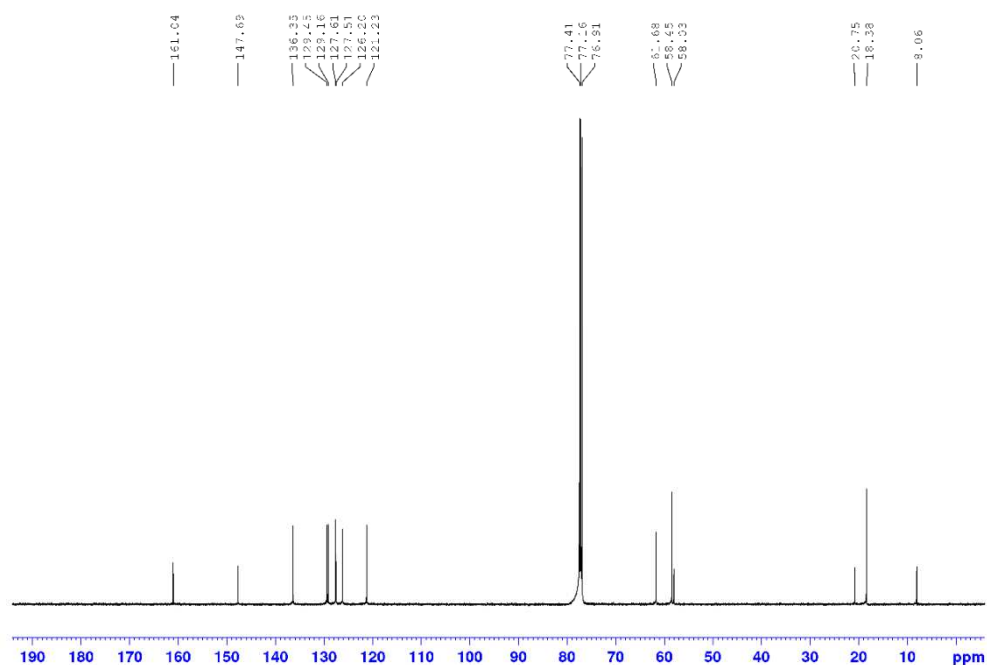


Figure S5.7.2: ^{13}C -NMR of **3** in CDCl_3 .

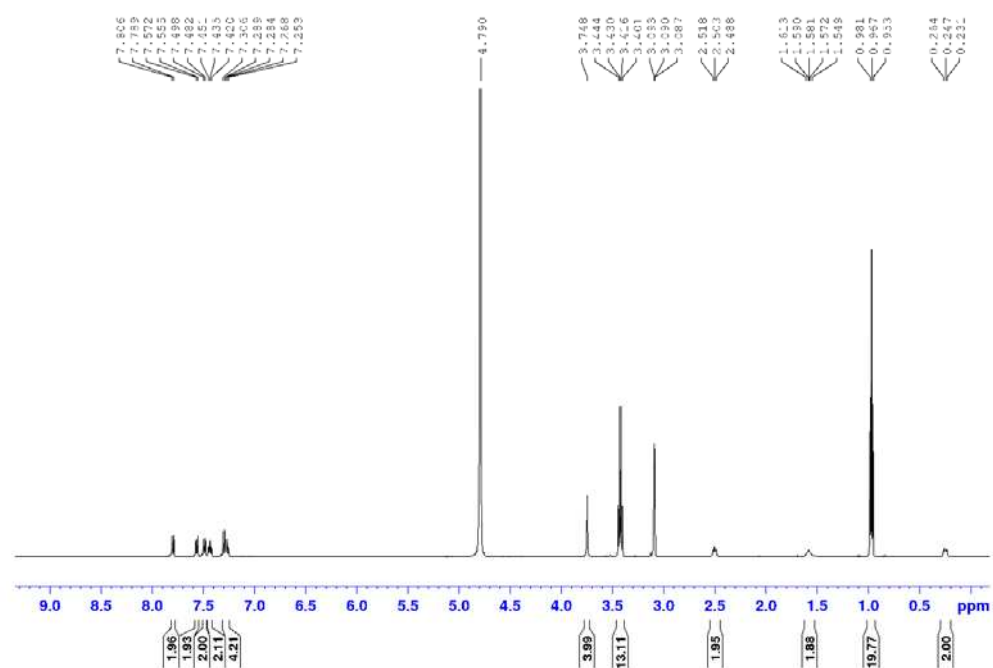


Figure S5.7.3: ^1H -NMR of **3-OD** in MeOD / 1M NaOD in D_2O with a ratio of 1:3.

5.8 ^1H - and ^{13}C -NMR of $[(1\text{a})\text{Re}(\text{CO})_3](\text{PF}_6)$

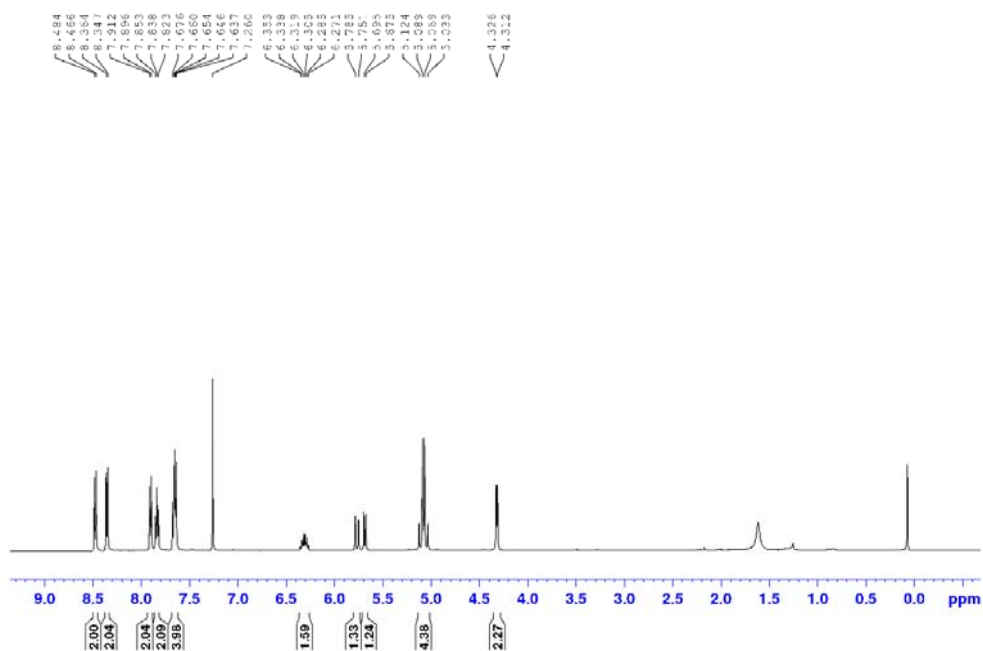


Figure S5.8.1: ^1H -NMR of $[(1\text{a})\text{Re}(\text{CO})_3](\text{PF}_6)$ in CDCl_3 .

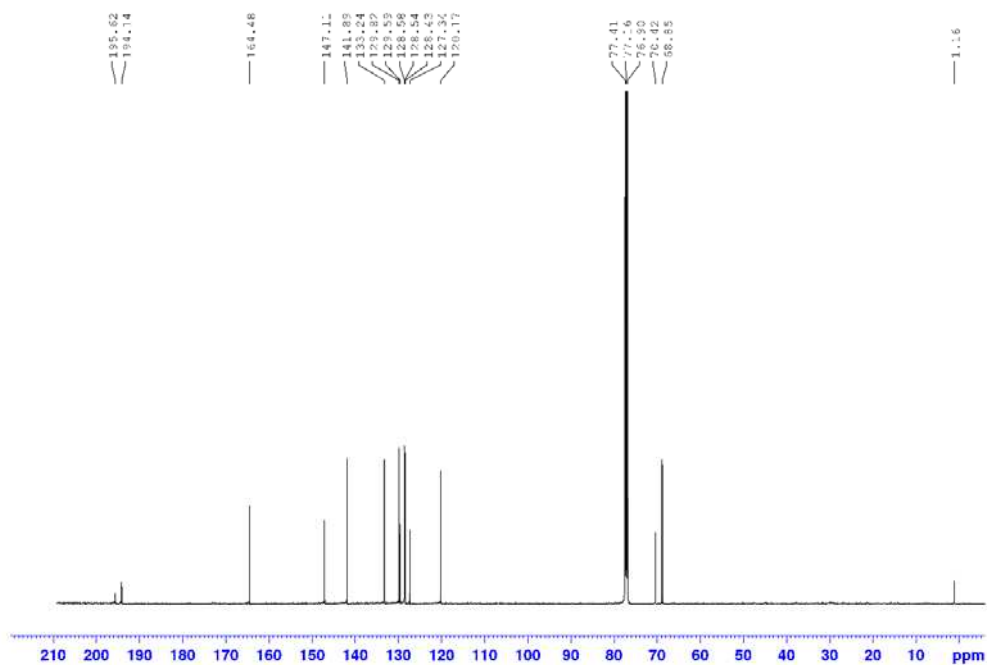


Figure S5.8.2: ^{13}C -NMR of $[(1\text{a})\text{Re}(\text{CO})_3](\text{PF}_6)$ in CDCl_3 .

5.9 ^1H - and ^{13}C -NMR of $[(\mathbf{1b})\text{Re}(\text{CO})_3](\text{PF}_6)$

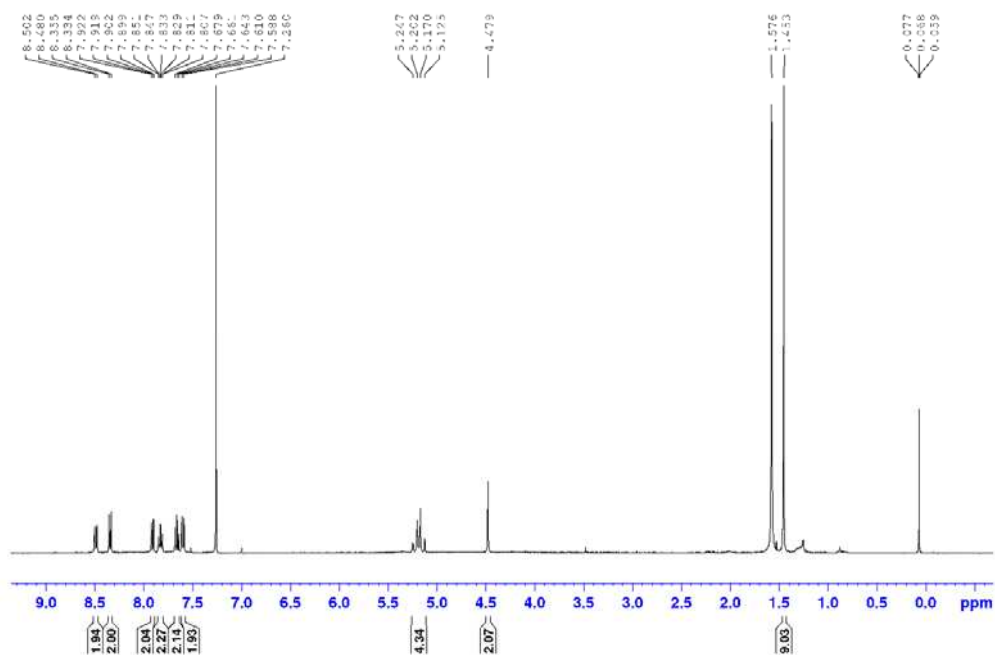


Figure S5.9.1: ^1H -NMR of $[(\mathbf{1b})\text{Re}(\text{CO})_3](\text{PF}_6)$ in CDCl_3 .

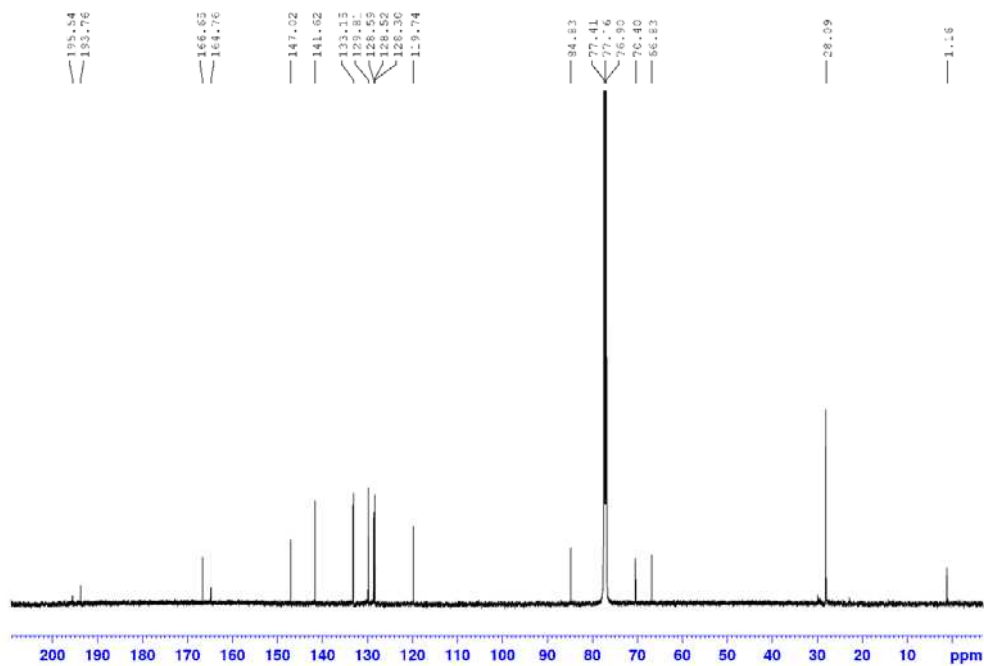


Figure S5.9.2: ^{13}C -NMR of $[(\mathbf{1b})\text{Re}(\text{CO})_3](\text{PF}_6)$ in CDCl_3 .

5.10 ^1H - and ^{13}C -NMR of $[(1\text{e})\text{Re}(\text{CO})_3](\text{PF}_6)$

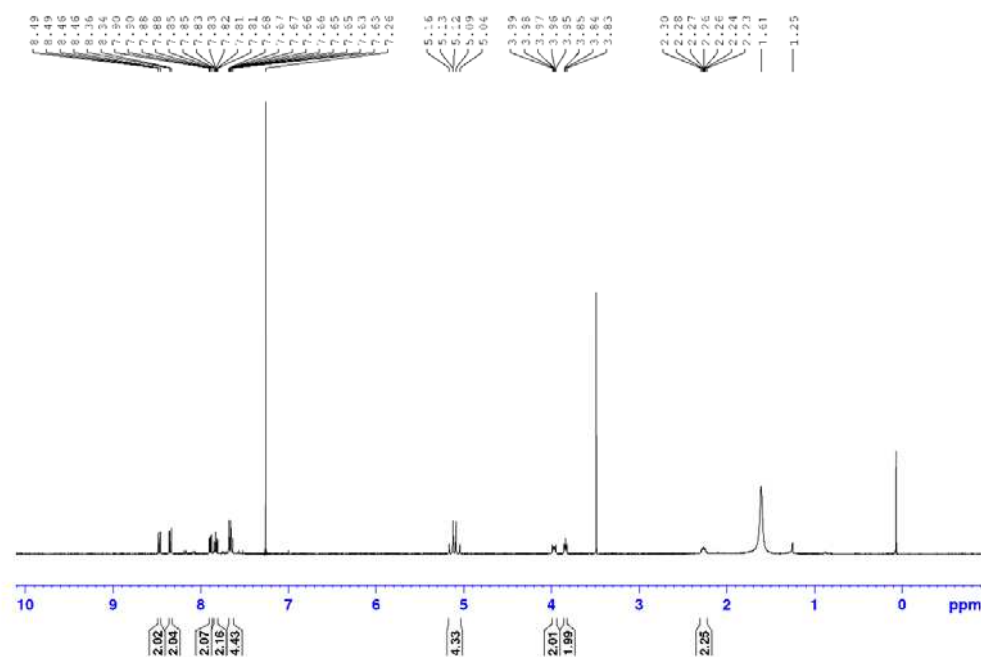


Figure S5.10.1: ^1H -NMR of $[(1\text{e})\text{Re}(\text{CO})_3](\text{PF}_6)$ in CDCl_3 .

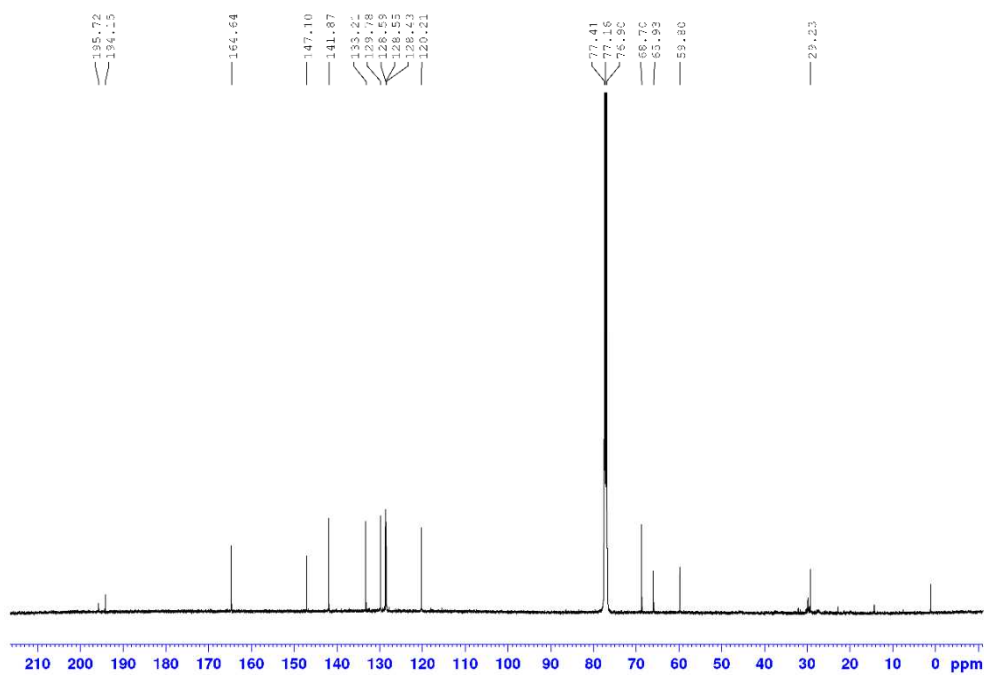


Figure S5.10.2: ^{13}C -NMR of $[(1\text{e})\text{Re}(\text{CO})_3](\text{PF}_6)$ in CDCl_3 .

5.11 ^1H - and ^{13}C -NMR of $[(3)\text{Re}(\text{CO})_3](\text{PF}_6)$ (**3-Re**)

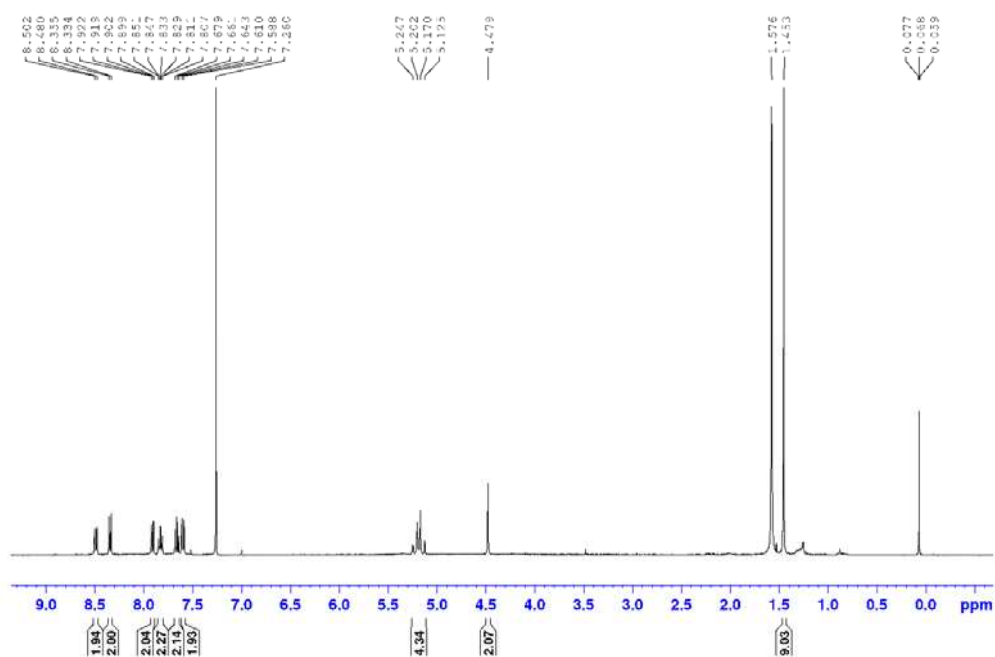


Figure S5.11.1: ^1H -NMR of **3-Re** in CDCl_3 .

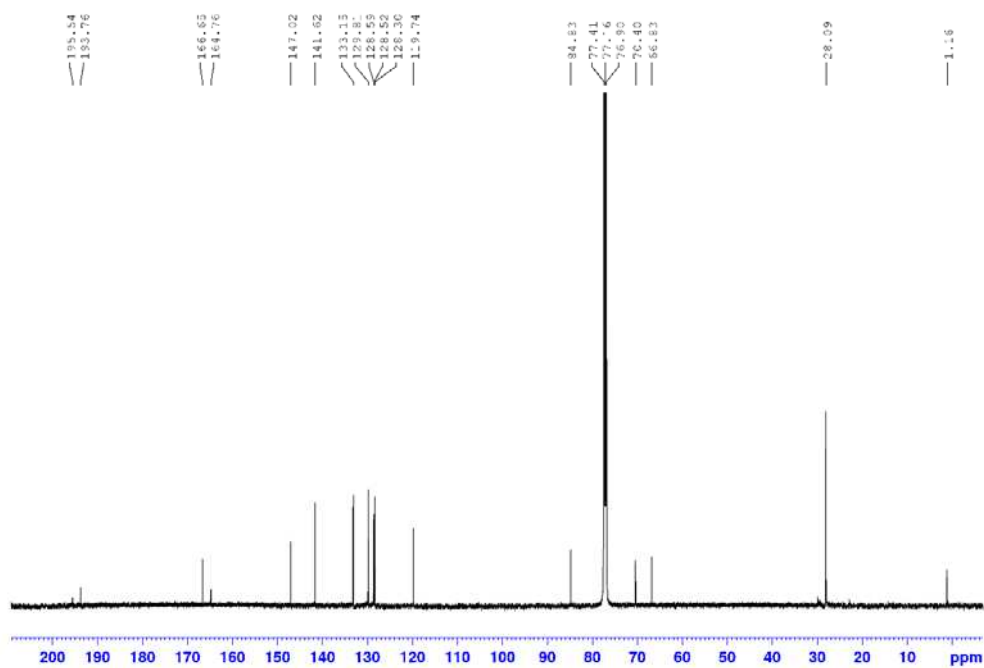


Figure S5.11.2: ^{13}C -NMR of **3-Re** in CDCl_3 .

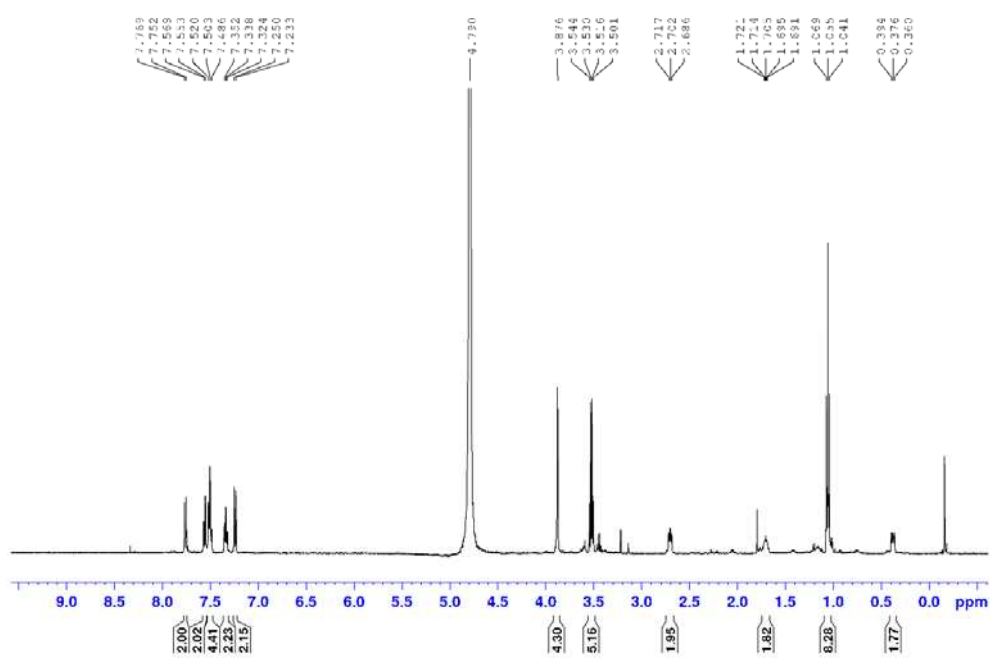


Figure S5.11.3: ^1H -NMR of **3@SBA** in 1M NaOD in D_2O .

6. Crystallographic Data

6.1 Crystal data and structure refinement for 1c

Empirical formula	C ₂₈ H ₂₃ ClF ₉ N ₃ O ₈
Diffractometer	XtaLAB Synergy, Dualflex, Pilatus 200K
Wavelength [Å]	1.54184
Formula weight	735.94
Crystal system	Monoclinic
Space group	P2 ₁ /m
a [Å]	7.06950(10)
b [Å]	18.0623(2)
c [Å]	12.10560(10)
α [°]	90
β [°]	97.1050(10)
γ [°]	90
Volume [Å ³]	1533.91(3)
Z	2
Density (calculated) [Mg/m ³]	1.593
Absorption coefficient [mm ⁻¹]	2.113
F(000)	748
Crystal size [mm ³]	0.250 x 0.100 x 0.050
Crystal description	brown plate
Theta range for data collection [°]	3.680 to 78.949
Index ranges	-9 ≤ h ≤ 7, -21 ≤ k ≤ 22, -12 ≤ l ≤ 15
Reflections collected	20113
Independent reflections	3361 [R(int) = 0.0258]
Reflections observed	3028
Criterion for observation	> 2 sigma(I)
Completeness to theta	99.9 % to 67.684°
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.81799
Data / restraints / parameters	3361 / 75 / 317
Goodness-of-fit on F ²	1.066
Final R indices [I > 2sigma(I)]	R1 = 0.0480, wR2 = 0.1391
R indices (all data)	R1 = 0.0534, wR2 = 0.1428
Extinction coefficient	n/a
Largest diff. peak and hole [e.Å ⁻³]	0.452 and -0.382
CCDC	1952828

In this structure, one trifluoroacetate anion forms a hydrogen bridge to another symmetry generated trifluoroacetate and the two TFA molecules share one proton. In the model, a half-occupied proton was placed on a calculated position (AFIX 147) next to the oxygen atom, which is involved in the hydrogen bonding. In this TFA molecule, the fluorine atoms are disordered on two sets of positions and were modelled in a ratio of 1:1. The two pyridine nitrogen atoms are protonated and both are hydrogen bonded to the same chloride at the position x+1, y, z with a distance of 3.2019(14) Å. This motif of doubly protonated pyridine rings pointing to a common hydrogen acceptor despite the presence of the more basic aliphatic nitrogen of the bispicolylamine has been described before.[8,9] The TFA molecule next to the chloride ion is four-fold disordered. As it is located very close to the mirror plane but not exactly on the mirror plane, this symmetry element already generates a TFA molecule that is disordered in a ratio of 1:1. Additionally, the fluorine atoms are disordered on two

sets of positions and were modelled in a ratio of 35:15. Suitable restraints for this TFA molecule had to be used (DFIX, RIGU and SADI). Furthermore, positive electron density between this trifluoroacetate molecule and the chloride anion (Figure S6.1.1) indicated that this TFA is actually present as an acid. This trifluoroacetic acid is hydrogen bonded to the already mentioned chloride at a distance that is typical for such carboxylic acid - chloride interactions (O33 - Cl1: 2.993(4) Å).[10] Therefore in this crystal structure, a TFA molecule is protonated and an aliphatic amine not, despite the fact that in solution the acid has a pKa value that is about 10 units lower than the amine! The overall crystal packing and the local environment of two pyridinium units next to the amine on the one side and one chloride ion next to the TFA on the other hand are all responsible for this special protonation scheme.

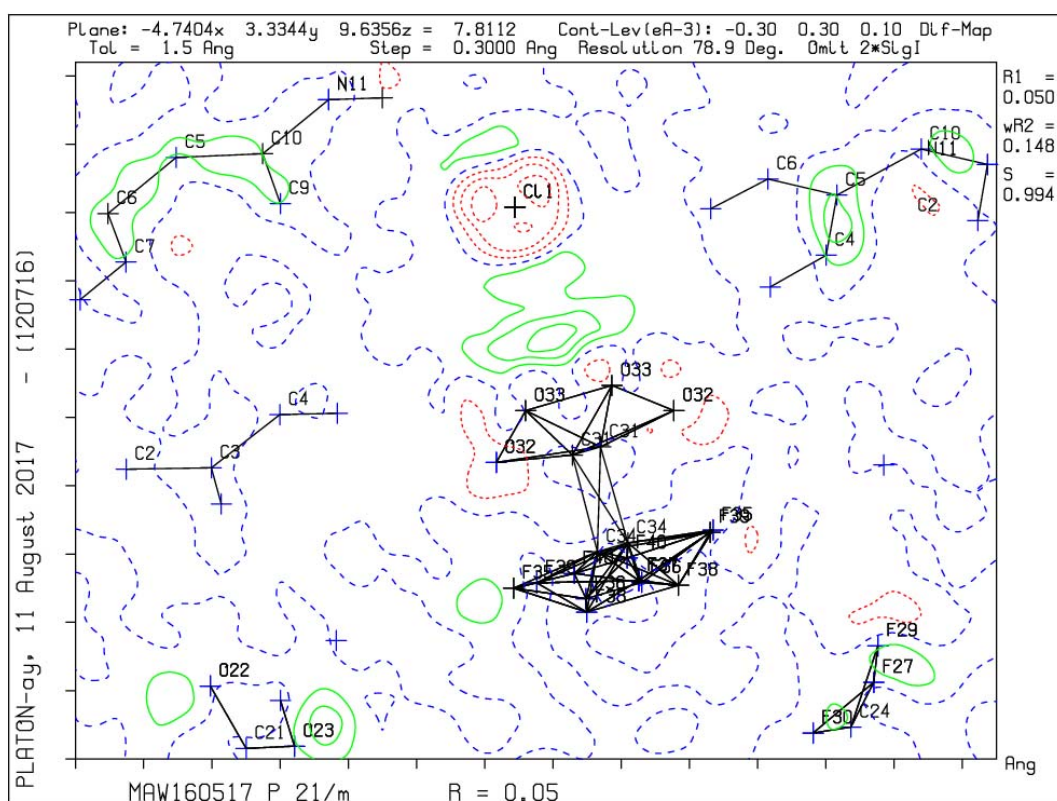


Figure 6.1.1: Positive electron density between the two symmetry equivalent positions of O33 of the four-fold disordered trifluoroacetate (TFA) molecule and Cl1 strongly suggest that the trifluoroacetate is actually present as an acid. The difference density map was calculated with the help of the program Platon.[11]

6.2 Crystal data and structure refinement for [(1a)Re(CO)₃](PF₆)

Empirical formula	C ₅₆ H ₅₀ F ₁₂ N ₆ O ₇ P ₂ Re ₂
Diffractometer	Xcalibur, Ruby
Wavelength [Å]	0.71073
Formula weight	1581.36
Crystal system	Monoclinic
Space group	P2 ₁
a [Å]	17.6463(6)
b [Å]	9.5745(2)
c [Å]	18.6548(7)
α [°]	90
β [°]	115.083(4)
γ [°]	90
Volume [Å ³]	2854.58(16)
Z	2
Density (calculated) [Mg/m ³]	1.840
Absorption coefficient [mm ⁻¹]	4.390
F(000)	1544
Crystal size [mm ³]	0.59 x 0.17 x 0.09
Crystal description	colorless stick
Theta range for data collection [°]	2.20 to 30.51
Index ranges	-24 ≤ h ≤ 25, -13 ≤ k ≤ 13, -26 ≤ l ≤ 26
Reflections collected	44314
Independent reflections	17390 [R(int) = 0.0347]
Reflections observed	15898
Criterion for observation	>2σ(I)
Completeness to theta	100.0 % to 30.51°
Absorption correction	Analytical
Max. and min. transmission	0.6934 and 0.1815
Data / restraints / parameters	17390 / 19 / 752
Goodness-of-fit on F ²	1.033
Final R indices [I > 2σ(I)]	R1 = 0.0327, wR2 = 0.0777
R indices (all data)	R1 = 0.0383, wR2 = 0.0815
Absolute structure parameter	-0.012(5)
Largest diff. peak and hole [e.Å ⁻³]	1.866 and -1.011
CCDC	1952827

6.3 Crystal data and structure refinement for [(1b)Re(CO)₃](PF₆)

Empirical formula	C ₃₃ H ₃₅ F ₆ N ₃ O ₆ Pre
Diffractometer	Xcalibur, Ruby
Wavelength [Å]	0.71073
Formula weight	900.81
Crystal system	Triclinic
Space group	P-1
a [Å]	11.7074(3)
b [Å]	12.2413(4)
c [Å]	12.8682(3)
α [°]	89.647(2)
β [°]	75.623(2)
γ [°]	88.455(2)
Volume [Å ³]	1785.79(9)
Z	2
Density (calculated) [Mg/m ³]	1.675
Absorption coefficient [mm ⁻¹]	3.525
F(000)	892
Crystal size [mm ³]	0.28 x 0.10 x 0.07
Crystal description	colorless stick
Theta range for data collection [°]	2.33 to 29.57
Index ranges	-15 ≤ h ≤ 16, -16 ≤ k ≤ 16, -17 ≤ l ≤ 17
Reflections collected	37899
Independent reflections	9941 [R(int) = 0.0642]
Reflections observed	8439
Criterion for observation	>2σ(I)
Completeness to theta	99.4 % to 29.57°
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7804 and 0.4353
Data / restraints / parameters	9941 / 0 / 454
Goodness-of-fit on F ²	1.029
Final R indices [I > 2σ(I)]	R1 = 0.0378, wR2 = 0.0789
R indices (all data)	R1 = 0.0498, wR2 = 0.0852
Largest diff. peak and hole [e.Å ⁻³]	1.870 and -0.806
CCDC	1952829

6.4 Crystal data and structure refinement for [(1e)Re(CO)₃](PF₆)

Empirical formula	C ₂₆ H ₂₃ F ₆ N ₃ O ₄ Pre
Diffractometer	XtaLAB Synergy, Dualflex, Pilatus 200K
Wavelength [Å]	0.71073
Formula weight	772.64
Crystal system	Monoclinic
Space group	P2 ₁ /c
a [Å]	17.3858(4)
b [Å]	9.8329(2)
c [Å]	17.3855(4)
α [°]	90
β [°]	110.109(2)
γ [°]	90
Volume [Å ³]	2790.92(11)
Z	4
Density (calculated) [Mg/m ³]	1.839
Absorption coefficient [mm ⁻¹]	4.489
F(000)	1504
Crystal size [mm ³]	0.119 × 0.106 × 0.071
Crystal description	colorless prism
Theta range for data collection [°]	2.375 to 30.508
Index ranges	-24 ≤ h ≤ 24, -14 ≤ k ≤ 14, -24 ≤ l ≤ 24
Reflections collected	128917
Independent reflections	8524 [R(int) = 0.0603]
Reflections observed	7691
Criterion for observation	> 2σ(I)
Completeness to theta	100.0 % to 25.242°
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7411 and 0.6172
Data / restraints / parameters	8524 / 0 / 371
Goodness-of-fit on F ²	1.047
Final R indices [I > 2σ(I)]	R1 = 0.0225, wR2 = 0.0503
R indices (all data)	R1 = 0.0275, wR2 = 0.0517
Extinction coefficient	n/a
Largest diff. peak and hole [e.Å ⁻³]	1.027 and -0.798
CCDC	1952830

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